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IF THE bird be full grown (at the time of operation) his crest grows fallow, he ceases to crow, and foregoes sexual passion; but if you cauterize the bird when young, none of these male attributes or propensities will come to him as he grows up. The case is the same with man: if you mutilate them in boyhood, the later growing hair never comes, and the voice never changes but remains high pitched; if they be mutilated in early manhood, the late growths of hair quit them except the growth in the groin, and that diminishes but does not entirely depart. The congenital growths of hair never fall out, for a eunuch never grows bald.

(RRT) Aristotle  
Historia Animalium

44600.



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## Creatinine Excretion in Women: Data Collected in the Course of Urinalysis for Female Sex Hor- mones<sup>1</sup>

### [Creatinine Excretion In Women]

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**D**URING THE PAST 10 YEARS this laboratory has been engaged in the quantification of female sex hormones and their excretory products in the urine of pregnant and non-pregnant women under various physiological, pathological and experimental conditions. Realizing the difficulty of procuring the full cooperation of patients and of hospital nursing staffs in obtaining accurately timed specimens, we have made it a routine to perform creatinine determinations upon all urines analyzed in order to detect gross errors in collection. This procedure is based upon Folin's accepted observation (1) that urinary creatinine is a product of endogenous metabolism and that the creatinine output for any given individual is relatively constant from day to day. With the exception of creatine determinations in the urines of 4 menstruating women, creatinine output alone has been measured, since no primary effort was being made to study creatine and creatinine metabolism in the subjects under observation. The large amount of data which has accumulated, however, contains information which may be of value in considering any

possible relationship between female sex physiology and creatinine excretion. Furthermore, analysis of the data has made it possible for us to evaluate the reliability of this method of checking urine collections and the feasibility of recalculating 24-hour volumes on the basis of the creatinine content of specimens in which gross errors are apparent.

#### METHODS AND RESULTS

Urinary creatine and creatinine have been measured according to the method of Folin (2). The methods utilized in the study of the excretion of female sex hormones and their excretory products have been described and most of the results reported and discussed in previous publications (3-11). The results on creatine and creatinine excretion included in this survey are exclusively from women in whom we were absolutely certain of the accuracy of collections. Twenty-four-hour volumes were obtained except where otherwise specified, and all results are expressed in terms of 24-hour excretion. No attempt was made to control the diet. No preservative was used but all specimens were kept cold during the period of collection and analyzed within 12 hours of the time of the last voiding.

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<sup>1</sup> The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by grants from the Committee for Research in Problems of Sex, National Research Council

### *Creatine and Creatinine Excretion During Menstrual Cycles*

From each of 6 menstruating women, repeated urines were obtained throughout 1 to 6 complete menstrual cycles, a total of 14 cycles involving 140 creatinine determinations. In the urines of 4 of these same women, creatine was also measured during a total of 11 cycles involving 113 determinations. The cyclic variations in estrogen excretion were measured in all 6 women, from which we conclude that only 2 of the 14 cycles were anovulatory.

O. W. S. (fig. 1, table 1) was studied throughout 6 complete cycles, creatine, creatinine and total estro-

secutive cycles. From the clinical history and the curves for urinary estrogen, we believe that conception and an early abortion took place during the first 38-day cycle and that this episode was followed by 2 anovulatory periods. The data on the 3d cycle are not included in the chart, since the values for all 3 constituents fall on the curves given in the second cycle. In each of the 3 cycles, 2 peaks of creatinine excretion occurred, one on the 9th to 12th days and a second 2 to 4 days before flow. As with O. W. S., creatinuria consistently accompanied the onset of flow and was absent at all other times.

The other two menstruating women studied, each

TABLE 1. CREATINE AND CREATININE EXCRETION DURING 6 CYCLES IN A NORMALLY MENSTRUATING INDIVIDUAL (O.W.S.)

| Day of Cycle | Cycle 1<br>5/5-6/3/34       |                 | Cycle 2<br>6/3-7/1/34       |      | Cycle 3<br>7/1-29/34 |      | Cycle 4<br>6/3-7/1/35       |      | Cycle 5<br>7/1-29/35 |      | Cycle 6<br>4/20-5/19/36 |      |
|--------------|-----------------------------|-----------------|-----------------------------|------|----------------------|------|-----------------------------|------|----------------------|------|-------------------------|------|
|              | P.C. <sup>1</sup>           | C. <sup>2</sup> | P.C.                        | C.   | P.C.                 | C.   | P.C.                        | C.   | P.C.                 | C.   | P.C.                    | C.   |
| 1            |                             |                 |                             |      | 1.44                 | 0.12 |                             |      |                      |      |                         |      |
| 2 } Men-     | 1.46                        | 0.30            | 1.45                        | 0.35 |                      |      |                             |      |                      |      |                         |      |
| 3 } struat-  |                             |                 |                             |      | 1.40                 | 0.42 |                             |      | 1.58                 | 0.40 |                         |      |
| 4 } ing      | 1.45                        | 0               | 1.43                        | 0.08 |                      |      |                             |      |                      |      |                         |      |
| 5            |                             |                 |                             |      |                      |      |                             |      | 1.62                 | 0    |                         |      |
| 6 or 7       | 1.34                        | 0               | 1.34                        | 0    | 1.33                 | 0    | 1.46                        | 0    | 1.51                 | 0    |                         |      |
| 8 or 9       |                             |                 |                             |      |                      |      | 1.50                        | 0    |                      |      |                         |      |
| 10 or 11     | 1.32                        | 0               | 1.36                        | 0    | 1.35                 | 0    | 1.45                        | 0    | 1.54                 | 0    |                         |      |
| 12 or 13     |                             |                 | 1.38                        | 0    | 1.40                 | 0    |                             |      | 1.50                 | 0    |                         |      |
| 14 or 15     | 1.36                        | 0               | 1.46                        | 0    | 1.46                 | 0    | 1.45                        | 0    | 1.43                 | 0    | 1.37                    | 0    |
| 16 or 17     |                             |                 |                             |      |                      |      | 1.52                        | 0    |                      |      |                         |      |
| 18 or 19     | 1.42                        | 0               | 1.46                        | 0    | 1.46                 | 0    | 1.50                        | 0    | 1.48                 | 0    | 1.54                    | 0    |
| 20 or 21     | 1.41                        | 0               | 1.47                        | 0    |                      |      |                             |      | 1.54                 | 0    |                         |      |
| 22 or 23     |                             |                 | 1.50                        | 0    |                      |      | 1.57                        | 0    | 1.57                 | 0    | 1.60                    | 0    |
| 24 or 25     |                             |                 | 1.52                        | 0    | 1.58                 | 0    | 1.71                        | 0    | 1.69                 | 0    | 1.71                    | 0    |
| 26 or 27     | 1.58                        | 0               |                             |      | 1.43                 | 0    | 1.62                        | 0.20 |                      |      |                         |      |
| 28 or 29     | 1.57                        | 0               | 1.58                        | 0    | 1.42                 | 0    | Continued<br>in next column |      | 1.60                 | 0    | 1.59                    | 0.12 |
| 1 } Men-     | Continued<br>in next column |                 | Continued<br>in next column |      | 1.44                 | 0    |                             |      | 1.55                 | 0.22 | 1.42                    | 0.20 |
| 3 } struat-  |                             |                 |                             |      | 1.45                 | 0.18 |                             |      |                      |      |                         |      |
| 4 } ing      |                             |                 |                             |      | 1.45                 | 0    |                             |      |                      |      |                         |      |

<sup>1</sup> P.C.=Preformed creatinine, gm. in 24 hr.

<sup>2</sup> C.=Creatine as creatinine, gm. in 24 hr.

gen being measured in each of 60 urine specimens. The curves of estrogen excretion indicated that all 6 cycles were ovulatory with a peak in total estrogen 12 to 14 days before the next catamenia. In each, the premenstrual drop in urinary estrogen was accompanied by a rise in urinary creatinine. Menstruation itself, at which time the lowest titers for urinary estrogen pertained, was consistently associated with creatinuria and a decrease in the output of creatinine. In this individual, creatine was never demonstrable in the urine except just before and during flow. Two other individuals (a total of 3 cycles involving 27 creatinine and estrogen determinations) showed curves similar to those just described, that is, a mid-cycle peak in estrogen excretion and a drop in the 24-hour creatinine output just before or at the start of menstruation. Creatine was not measured.

L. D. Y. (fig. 2) was followed throughout 3 con-

throughout one cycle, showed curves of estrogen excretion indicative of ovulation. In each, the creatinine curve followed the general pattern of those illustrated in figure 2 on L. D. Y. One of them excreted creatine throughout the cycle followed, but the amount during the luteal phase, 60 to 80 mg. in 24 hours, was consistently less than that during menstruation and follicle ripening, 180 to 340 mg. in 24 hours. The other individual excreted 30 to 200 mg. of creatine in 24 hours during the first half of a 31-day cycle, but after the 19th day, although daily specimens were analyzed, no creatine was found until the day before the onset of the next period.

The results described are sufficiently consistent to suggest strongly that some correlation exists between fluctuations in creatine and creatinine excretion and ovarian activity. In all 14 cycles, a rise in creatinine excretion occurred late in the second half

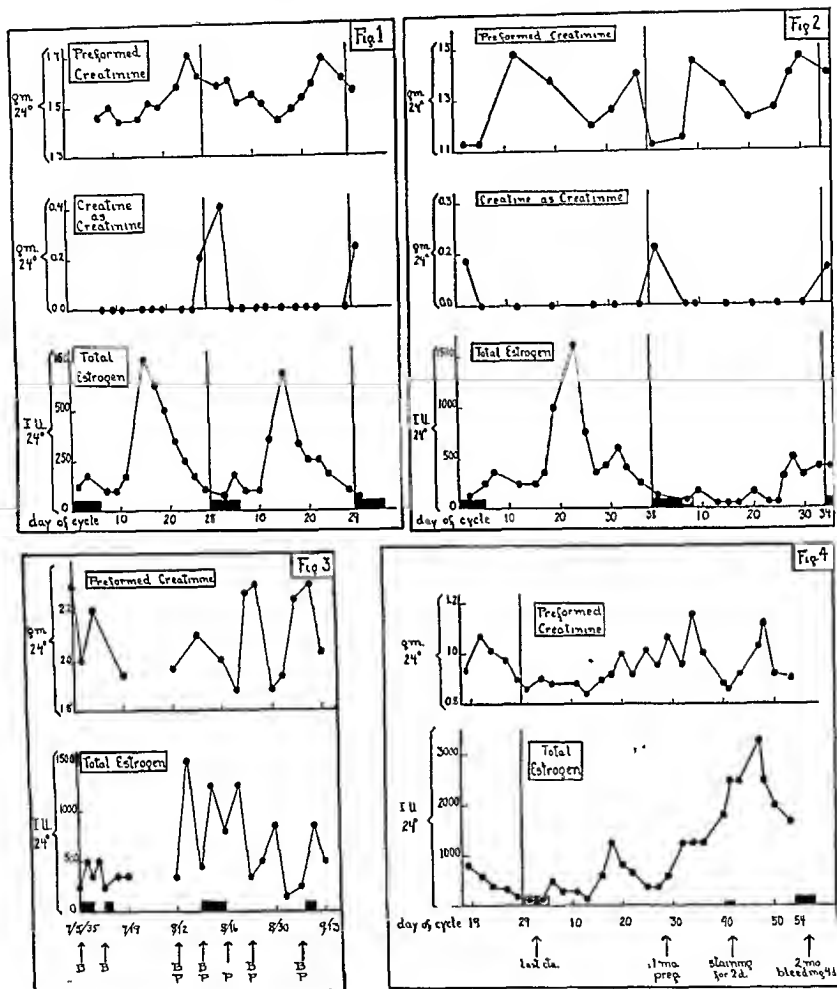


FIG. 1. CREATININE, CREATINE AND ESTROGEN EXCRETION DURING CONSECUTIVE OVULATORY CYCLES ON O. W. S. FIG. 2. CREATININE, CREATINE AND ESTROGEN EXCRETION DURING CONSECUTIVE CYCLES ON L. D. T. PROBABLY AN EARLY ABORTION FOLLOWED BY ANOVULATORY CYCLE. FIG. 3. CREATININE AND ESTROGEN EXCRETION BEFORE AND DURING THE ADMINISTRATION OF PITUITARY GONADOTROPIN TO A PATIENT (MRS. A. G.) WITH IRREGULAR CATAMENIA, OBESITY AND MASCULINE HIRAUTISM.

and a decreased output preceded or accompanied the onset of flow. In 3 of the 6 women studied, a total of 5 cycles, a post-menstrual rise, fully as marked as that during the second half of the cycle, was observed. In 2 of the 4 women in whom urinary creatine was meas-

ured, creatinuria appeared only at the onset of flow (9 cycles). The other two (2 cycles) excreted creatine in larger amounts at this time than during the luteal phase. In one individual (L. D. T., fig. 2), the same pattern of creatine and creatinine excretion pertained

throughout 3 consecutive cycles, despite the fact that the first of these (according to the curve of estrogen excretion) was ovulatory and the other 2 anovulatory. We are led to believe, therefore, that any cyclic changes in creatine and creatinine metabolism may be considered the direct result not of ovarian secretion but rather of other changes, e.g., vascular and those of water and salt metabolism, which characterize the menstrual phenomenon, whether or not menstrual flow follows corpus luteum regression. Our studies of estrogen metabolism in women have indicated that increased destruction of estrogen pertains at the onset of both ovulatory and anovulatory bleeding and may be the precipitating cause of the vascular phenomena which are associated with endometrial breakdown (7). Any effect of ovarian hormones, therefore, upon creatine and creatinine excretion, may depend upon shifts in their metabolism rather than upon the amounts and kinds secreted or administered.

In the various reviews on creatine and creatinine metabolism, the conclusion has been generally reached that fluctuations in the urinary excretion of these 2 compounds by women bear no relationship to the menstrual cycle. This has been based largely on 4 papers (12-15) published between the years 1911 and 1921. Because our own findings do not agree with this conclusion, it seems worthwhile to review these publications in some detail.

Krause (12) in 1911, studied creatine and creatinine excretion in relation to the menstrual cycle in 7 women. In 5 of the 7 cases, only 2 to 4 random specimens were analyzed and in the other 2, upon whom the most work was done (i.e., 14 specimens from each), collections were scattered over a 6-month interval. No urines were obtained during menstruation. It is difficult to draw any conclusions on the basis of such scattered data. Krause's observation, however, that creatine was present in all urines just after menstruation and was absent or present only in traces in most cases 2 or 3 weeks after the period is in general agreement with the findings noted above in our cases in whom creatinuria was followed.

Rose (13) in 1917, studied creatine and creatinine in the urine of 6 normal women, daily specimens being collected from each over 18 to 32-day intervals, including a total of 8 catemenia. She concluded that no correlation exists between menstrual cycles and creatine and creatinine output. From an examination of her figures it is apparent that none of the subjects collected complete 24-hour specimens, since the daily creatinine excretion of each showed such wide fluctuations; in *subject 1* the values varied between 85 and 356 mg. Moreover, the ratios of creatine to creatinine in all of the specimens are very much higher than those found anywhere in the literature on creatine and creatinine excretion, for example, 242 mg. of creatine in a specimen containing only 266 mg. of creatinine. We would be inclined to doubt the value of any conclusions based on data which differ so markedly from those of other investigators.

Rose, Dimmitt and Bartlett (14) in 1918, followed urinary creatine and creatinine daily from 2 normally men-

struating individuals for 14 and 13 days, respectively. With one of the subjects, collections started on the day after menstruation ended. Ten of the 14 specimens contained creatine, the largest amount, 160 mg. in 24 hours, occurring in the first specimen obtained just after flow. During the rest of the period studied, the amounts varied between 0 and 70 mg. in 24 hours. Creatinine excretion (1.12 to 1.22 gm. in 24 hours) showed no cyclic variation during these 14 intermenstrual days. The other subject was followed for 13 days starting 3 days before menstruation and including the menstrual specimens. Ten of the 13 specimens contained creatine, the largest amounts (8 and 90 mg. in 24 hours) being found in the 2 immediately premenstrual specimens, the other 11 specimens containing 0 to 60 mg. in 24 hours. Creatinine excretion varied between 0.98 and 1.15 gm. in 24 hours, a definite peak being apparent on the last 3 days before menstruation together with a marked drop at the start of flow. The findings of these 2 cases, therefore, are in general agreement with our observations, although the authors naturally draw no conclusions from such meager data.

Stearns and Lewis (15) in 1921, analyzed the urines of 3 normally menstruating women for creatine and creatinine at frequent intervals throughout a total of 8 menstrual cycles. In the course of this investigation, dietary measures were introduced and both creatine and creatinine were ingested sporadically. The authors concluded that no relationship existed between menstruation and creatine or creatinine excretion. However, in *subject S.*, upon whom the most complete studies were performed, urinary creatine was demonstrable only around the time of the menses in 3 of the 5 cycles followed (except when creatine was ingested). Creatinuria in the absence of creatine ingestion appeared intermenstrually in this subject during 1 cycle when she was "ill and overstrained" and during another when she was on a high-protein diet. During 2 complete consecutive cycles on this subject, when she was in good health and on a normal diet, the curves for both creatine and creatinine excretion, if one omits the values on those days when creatine or creatinine were ingested, are entirely similar to those on *O. W. S.* above.

The results on the 6 women studied by us, therefore, confirm findings recorded by previous investigators. It is possible that in some women fluctuations in creatine and creatinine excretion occur which are not related to menstruation and which would obscure the menstrual changes or make them seem of no significance. The repeated observation, however, both in our own data and those of others, that menstruation is associated with an increased creatinuria and a drop in creatinine excretion would appear to be indicative of some relationship between menstruation and creatine and creatinine metabolism.

The values for 24-hour creatinine excretion on these 6 menstruating women are summarized in table 2. The data illustrate the degree of fluctuation in creatinine output which may be expected in normally menstruating women. In no instance was the

coefficient of variation greater than 10.9% or the maximum deviation from the mean value greater than 21.4%

### Creatinine Excretion in Women with Gynecological Disorders

**Effect of hormone administration** Five women with various menstrual abnormalities have been followed, in 4 of whom the effect of hormone administration has been observed. The estrogenic and gonadotropic potencies of the urines were measured as well as the creatinine content.

Seven consecutive specimens were studied from Mrs A. M., aged 32, a case of amenorrhea of 8 years' duration.

been interrupted by the injection. On days 31 and 33 the tests for urinary FSH gave positive pregnancy reactions, no gonadotropic activity having been previously demonstrable. An endometrial biopsy on the day before flow, which was profuse, showed early decidua. Urinary estrogens varied between 300 and 1,650 i. u. per 24 hour volume, the curve of excretion being entirely similar to that shown during what may have been a spontaneous early abortion in L. D. T. (fig. 2). The curve for urinary creatinine, with values between 1.20 and 1.53 gm. in 24 hours, was suggestive of the 2 peak type, although less uniform than those recorded above. No correlation was apparent between creatinine excretion and the injection of the pituitary gonadotropin extract, but a drop in creatinine excretion accompanied the onset of flow.

TABLE 2 CREATININE EXCRETION IN 6 MENSTRUATING WOMEN

| Subject         | No of Specimens | No of Cycles | Range of Values | Mean Value and Std. Dev. | Coef of Var | Maximum Deviation |      |
|-----------------|-----------------|--------------|-----------------|--------------------------|-------------|-------------------|------|
|                 |                 |              |                 |                          |             | gm                | %    |
| EEJ             | 21              | 2            | 1.21-1.69       | 1.45 ± 0.12              | 8.3         | 0.24              | 17.5 |
| OWS             | 60              | 6            | 1.32-1.71       | 1.48 ± 0.09              | 6.0         | 0.23              | 15.5 |
| LDY             | 20              | 3            | 1.12-1.48       | 1.31 ± 0.13              | 9.9         | 0.19              | 14.5 |
| HS <sup>1</sup> | 6               | 1            | 1.00-1.14       | 1.05 ± 0.05              | 4.8         | 0.09              | 8.5  |
| LG              | 9               | 1            | 1.00-1.33       | 1.19 ± 0.13              | 10.9        | 0.19              | 15.9 |
| SS <sup>2</sup> | 24              | 1            | 0.80-1.08       | 0.89 ± 0.08              | 9.0         | 0.19              | 21.4 |

<sup>1</sup> Based on analyses of 48 hour volumes of urine

<sup>2</sup> Based on analyses of 8 hour specimens collected from 11 P.M. to 7 A.M.

The patient weighed 93 pounds. The creatinine varied over rather narrow limits (0.78 to 0.91 gm. in 24 hours) and bore no relationship to rather marked fluctuations in the levels of follicle stimulating hormone (0 to 90 R. U. in 24 hours) and of total estrogen (75 to 250 I. U. in 24 hours).

Six specimens were analyzed from Miss M. C. during the years 1936 to 1941, complete hysterectomy with castration having been performed in 1933. The 4 specimens collected when no hormones were being administered, the last on Feb. 6, 1941, contained 1.20 to 1.27 gm. of creatinine, 30 to 50 I. U. of total estrogen and around 100 R. U. of follicle stimulating hormone (FSH) per 24 hour volume. Five mg. of estrone (50,000 I. U.) in oil were injected intramuscularly on Feb. 10, 1941. The 2 specimens collected immediately thereafter contained 2.450 and 400 I. U. of total estrogen, respectively, no demonstrable FSH, and 1.27 and 1.21 gm. of creatinine per 24 hour volume. It is apparent that creatinine excretion, within the time limits of this experiment, was not affected by this large single injection of estrone, despite the marked changes in hormone output.

Mrs M. S., a sterility case with irregular and scanty catamenia, was followed during a 41 day cycle (14 specimens), on the 33rd day of which a single injection of pituitary gonadotropin<sup>2</sup> was given intravenously. From the clinical data together with the curves of hormone excretion, we believe that a beginning pregnancy may have

The data on Mrs A. G., a case of obesity (weight 239 lb.) and marked masculine hirsutism, with long intervals of amenorrhea, are presented in figure 3. Over a period of 6 weeks, 5 intravenous injections of pituitary gonadotropin were given. Endometrial biopsies, which in 4 of 6 instances were followed by bleeding of 2 to 7 days' duration, showed both before and during injections the same picture, namely, early proliferation. Each injection was followed by a marked rise in estrogen excretion. Urinary FSH was demonstrable on 3 occasions, once before and twice during injections. The fluctuations in urinary creatinine bore no apparent relationship either to the injections, the estrogen and FSH excretion or to the endometrial bleeding.

Mrs B. V. A., a case of typical functional uterine bleeding, was studied over a 7 year interval, during which time the effects of chorionic gonadotropin,<sup>3</sup> progesterone, estrone and estrinol administration were investigated. Of the 24 specimens analyzed, the creatinine values of 10 have had to be discarded, since the accuracy of hospital collections could not be relied upon except when a retention catheter was employed. However, there is sufficient data to indicate that neither chorionic gonadotropin<sup>3</sup> (5 cc daily on 3 successive days), progesterone (30 mg. over 3 days on 1 occasion and 75 mg. over 3 days on another), estrone (100,000 I. U. over 2 days), nor estrinol (0.5 to 2.0 mg. by mouth daily for 3 months) had any significant effect

<sup>2</sup> Gonadotropic extract of sheep pituitaries (Prephyns) Chappel Laboratories, Rockford, Illinois

<sup>3</sup> Chorionic gonadotropin (Antuitrin S), Parke, Davis and Company, Detroit, Michigan



upon creatinine excretion. Despite the marked effect of these hormones upon the endocrine balance, as evidenced by the changes in estrogen excretion following therapy, the range of creatinine values when the patient was receiving no hormones were practically the same (0.83 to 1.03 gm. in 24 hours in 8 specimens) as when they were being administered (0.88 to 1.04 gm. in 24 hours in 6 specimens). Creatinine excretion in this woman also bore no apparent relationship to menstrual flow, the range of values being the same whether the patient was bleeding profusely, staining or was in an amenorrheic stage.

It is conceivable that if creatine determinations had been performed upon the specimens from these women to whom hormones were administered, some more definite effect upon creatine and creatinine metabolism might have been apparent. Beard (16), for example, found

creatinine output of this individual, although Koven and Beard (19) observed an initial increase followed by a decrease in urinary creatinine following progesterone administration to normal rats.

Schrire and Zwarenstein (20) found that chorionic or pituitary gonadotropic extracts produced an increased creatinine output in normal rabbits but had no effect upon the already high creatinine excretion of castrates. Three of our subjects, none of whom was castrated, received gonadotropic extracts. In Mrs. M. S. a single intravenous injection of a potent pituitary preparation during the cycle of probable conception was followed by a continued rise in estrogen excretion, after which there was a precipitous drop and bleeding. No change in creatinine output could be correlated with the injection. Mrs. A. G., who received 5 intravenous injections of this same prep-

TABLE 3. CREATININE EXCRETION IN 5 WOMEN WITH GYNECOLOGICAL DISORDERS (4 of these were treated with sex hormones). Demonstrating that creatinine excretion is as constant under these conditions as in normally menstruating women (cf. Table 2)

| Subject | Clinical Condition            | No. of Specimens | Dates of Specimens | Hormonal Treatment                               | Range of Values         | Mean Value         | Stand. Dev. | Coef. Var. | Maximum Deviation |           |
|---------|-------------------------------|------------------|--------------------|--|-------------------------|--------------------|-------------|------------|-------------------|-----------|
| A M.    | Complete amenorrhea           | 7                | 11/2-9/34          | 0  | gm./24 hr.<br>0.78-0.91 | gm./24 hr.<br>0.81 | gm.<br>0.05 | %<br>6.3   | gm.<br>0.10       | %<br>12.3 |
| A.G.    | Sterility, obesity, hirsutism | 15               | 7/5-9/13/35        | Pit. gonadotropin                                | 1.89-2.32               | 2.11               | 0.17        | 8.0        | 0.22              | 10.4      |
| M.C.    | Menopause                     | 6                | 1936-1941          | Estrone  | 1.20-1.27               | 1.24               | 0.03        | 2.4        | 0.03              | 2.4       |
| M.S.    | Conception and early abortion | 14               | 6/25-8/9/35        | Pit. gonadotropin                                | 1.20-1.53               | 1.36               | 0.11        | 8.1        | 0.17              | 12.5      |
| B.V.A.  | Metrorrhagia                  | 14               | 1934-1941          | Ch. gonadotropin, progesterone, estrone, estriol | 0.83-1.04               | 0.95               | 0.07        | 7.4        | 0.12              | 12.6      |

that the injection of male and female sex steroids into rats resulted in an increased creatinuria, while no definite effect upon creatinine excretion was demonstrable. Williamson and Gulick (17), working with male rabbits, found that testosterone raised muscle creatine and decreased creatinuria, whereas, within the time and dosage limits of their experiments, creatinine metabolism was not affected.

Sharpey-Schafer and Schrire (18) reported that large daily injections of estradiol benzoate (100,000 I.U.) or of diethylstilbestrol (10 mg.) had no effect upon creatinine excretion in normal women but decreased the 24-hour output in menopausal women and castrates. In M. C., the castrate in our series, we observed no such effect, although hormone excretion was markedly altered. However, only a single injection of 5 mg. of estrone was given. B. V. A., the case of functional bleeding, received larger amounts of estrogen over longer periods with no significant effect upon creatinine excretion, although marked increases in estrogen output resulted. Furthermore, large daily injections of progesterone (10 to 25 mg.) temporarily stopped excessive bleeding and decreased the rate of estrogen destruction but did not demonstrably alter the

aration over a 6-week interval, during which no ovulation occurred, showed marked fluctuations in estrogen excretion related to the injections but no consistent change in creatinine output. With Mrs. B. V. A., excessive flowing ceased and estrogen output increased with chorionic gonadotropin injections but urinary creatinine was not demonstrably affected.

Our observations were incidental to the study of female sex hormone metabolism and may not be interpreted as signifying that creatinine metabolism is uninfluenced by sex hormone administration in women. They do indicate, however, that amounts of these hormones sufficient to cause physiological changes in women and markedly to affect hormone excretion do not result in any consistent or significant changes in creatinine output. Any fluctuations in creatinine excretion which followed hormone administration probably did not result from the hormones, since the range of these fluctuations was no greater than that observed in the same individuals when no hormones were being given. Moreover, in the sum-

TABLE 4 CREATININE EXCRETION IN 10 NORMALLY PREGNANT WOMEN

|     | Stage of Pregnancy | No of Specimens | Range of Values | Mean Value and Std Dev | Coef of Var | Maximum Deviation |      |
|-----|--------------------|-----------------|-----------------|------------------------|-------------|-------------------|------|
|     |                    |                 |                 |                        |             | gm                | %    |
|     | weeks              |                 | gm/24 hr        | gm/24 hr               | %           |                   |      |
| LDY | 5-37               | 11              | 1 11-1 45       | 1 31±0 11              | 8 6         | 0 20              | 15 3 |
| OWS | 5-33               | 6               | 1 30-1 72       | 1 50±0 14              | 9 3         | 0 26              | 17 4 |
| EBF | 16-39              | 10              | 0 86-1 19       | 0 98±0 10              | 10 2        | 0 21              | 21 5 |
| PP  | 26-term            | 13              | 1 04-1 41       | 1 17±0 10              | 8 5         | 0 24              | 20 5 |
| CP  | 12-38              | 6               | 1 00-1 34       | 1 20±0 15              | 12 5        | 0 20              | 16 6 |
| AP  | 12-39              | 7               | 1 14-1 51       | 1 31±0 13              | 9 9         | 0 20              | 15 3 |
| RC  | 26-term            | 12              | 1 22-1 76       | 1 40±0 16              | 11 4        | 0 35              | 25 0 |
| GRW | 10-31              | 6               | 0 81-1 15       | 0 96±0 10              | 10 4        | 0 19              | 19 8 |
| DL  | 7-26               | 5               | 1 14-1 37       | 1 28±0 09              | 7 0         | 0 14              | 10 9 |
| DG  | 18-38              | 4               | 1 15-1 42       | 1 30±0 11              | 8 4         | 0 15              | 11 6 |

mary of creatinine results on nonpregnant women presented in tables 2 and 3, it is apparent that the coefficients of variation and the maximum deviations from the mean values in those women to whom hormones were administered are no greater than in those who received no injections

#### Creatinine Excretion During Conception and Threatened Abortion

Two cases, L D Y and M S were followed through what appeared to be the period of conception with abortion prior to the second missed period. In both, a drop in creatinine excretion preceded flow and seemed to be more directly associated with bleeding than with estrogen excretion. The results in a third patient, Mrs Y B, are presented in figure 4 and include observations over the last 10 days prior to the cycle of conception and the first 54 days of a pregnancy complicated by threatened abortion. Hormone excretion was followed during this interval and also throughout the rest of pregnancy, which was normal. The 5 specimens collected before the last catamenia showed a late cycle peak in creatinine excretion and a drop before and at the onset of flow (This constitutes the 8th case and the 16th cycle in which this change in creatinine excretion has been observed in association with menstruation). During the month of conception, although estrogen excretion followed the curve indicative of ovulation, there was no peak and drop in creatinine. There was, however, a peak in creatinine excretion on the 35th day followed by a marked drop prior to an episode of staining on the 41st and 42nd days. This rise and fall in creatinine excretion again occurred preceding a second and more alarming episode of staining at the time of the second missed period.

The findings in this case indicate again that, although there is no direct relationship between ovarian activity and creatinine excretion, some change in creatinine metabolism is associated with uterine bleeding. The marked hormonal changes which accompany early pregnancy (chorionic gonadotropin

was excreted by this woman in rapidly increasing amounts between the 35th and 54th days) did not affect the levels of creatinine. The average creatinine excretion during the 10 days before the cycle of conception was 0 98 gm in 24 hours with a coefficient of variation of 7 1%. The mean value of the 22 specimens collected during the first 54 days of pregnancy was 0 94 gm in 24 hours with a coefficient of variation of 8 5%.

#### Creatinine Excretion During Normal Pregnancy

Ten women carefully instructed and trained in the accurate collection of 24 hour volumes of urine have been followed with repeated specimens during pregnancy, a total of 80 determinations. In these 10 normal cases, urinary pregnanediol, estrogens and chorionic gonadotropin followed the general curves

TABLE 5 CREATININE EXCRETION IN 4 WOMEN DURING FIRST AND SECOND STAGES OF LABOR

| Sub<br>ject | Creatinine Excretion before Labor   |                                   |                   | Creatinine Excretion during Labor  |  |
|-------------|---|-----------------------------------|-------------------|--|--|
|             | Stage of pregnancy  | No of specimens                   | gm/24 hr          | Hours of labor covered   | gm/24 hr   |
| R C         | 26 wk to term<br>1 wk before labor  | 12 <sup>v</sup><br>1 <sup>v</sup> | 1 22 1 76<br>1 30 | 1st 6 <sup>v</sup><br>6th to 13th <sup>v</sup><br>13th to 20th <sup>v</sup><br>20th to 10th <sup>v</sup><br>30th to 37th <sup>v</sup><br>37th to 41st <sup>v</sup><br>last 5 of 46 hr labor <sup>v</sup> | 1 33<br>0 68<br>1 12<br>0 97<br>1 02<br>0 76<br>0 61 |
| P P         | 26 wk to term<br>3 days before labor  | 13 <sup>v</sup><br>1 <sup>v</sup> | 1 04-1 41<br>1 25 | 1st 6 <sup>v</sup><br>6th to 12th <sup>v</sup><br>12th to 20th <sup>v</sup><br>last 6 of 26 hr labor <sup>v</sup>  | 1 20<br>1 30<br>0 80<br>0 79                         |
| A C         | 36 to 32 hr before<br>mechanical in<br>duction<br>last 12 hr before<br>induction<br>(labor started immediately after artificial rupture of membranes) | 1 <sup>v</sup><br>1 <sup>v</sup>  | 1 08<br>1 02      | 1st 2 <sup>v</sup><br>last 3 of 5 hr labor <sup>v</sup>  | 0 57<br>0 65   |
| P L         | (not followed before labor started)   |                                   |                   | 1st 2 <sup>v</sup><br>3rd to 5th <sup>v</sup><br>7th to 9th <sup>v</sup><br>last 6 of 23 hr labor <sup>v</sup>   | 1 02<br>1 03<br>0 77<br>0 63                         |

<sup>v</sup> Voided specimen  
<sup>c</sup> Catheter specimen

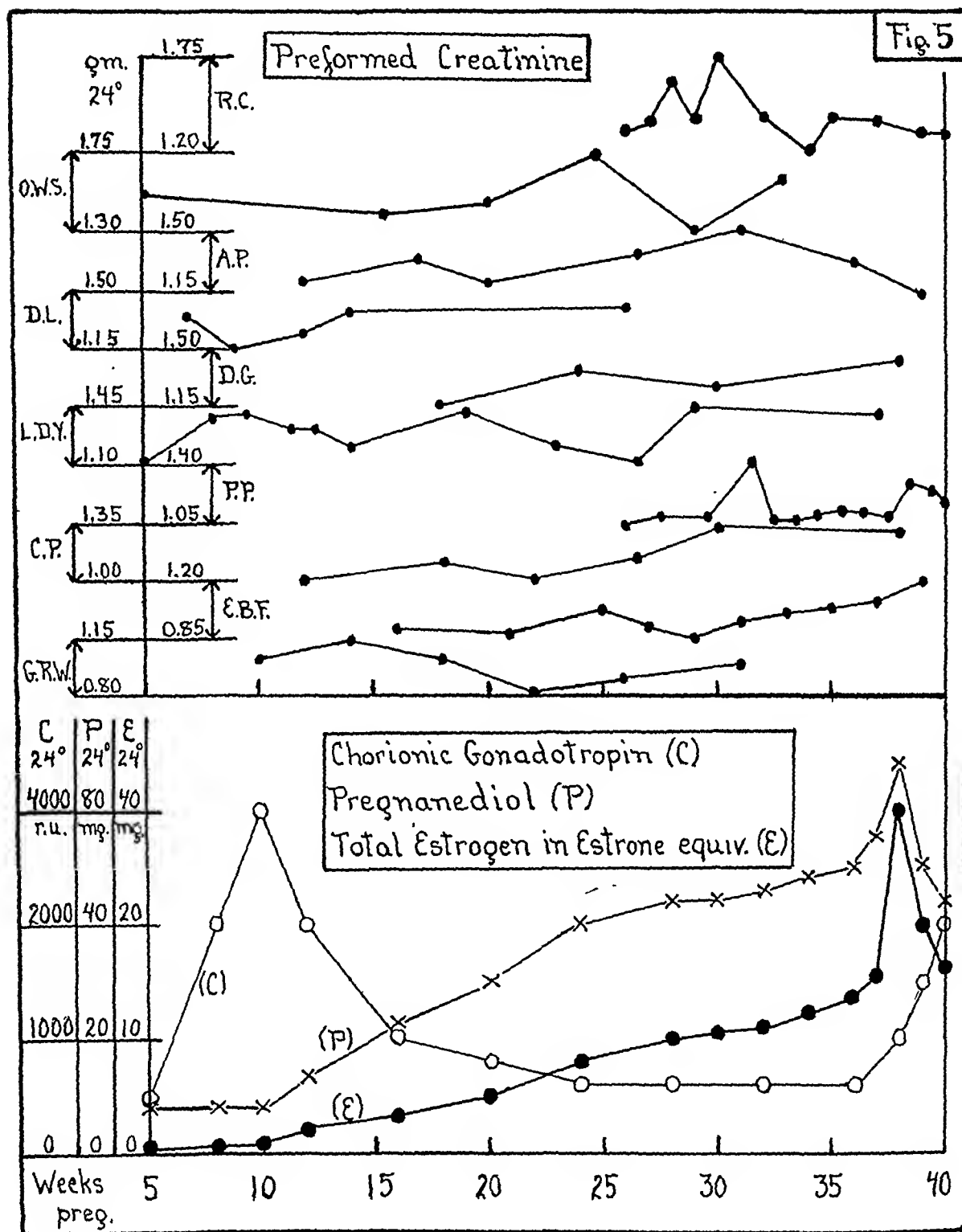


FIG. 5. Creatinine excretion during 10 normal pregnancies together with composite curves of hormone excretion throughout normal pregnancies.

previously published by us (4, 5, 11) and graphically presented in the lower part of figure 5, although the actual levels of excretion varied with individuals. The fluctuations in creatinine excretion were of the same order as those observed in nonpregnant women and bore no apparent relationship to the endocrine bal-

ance as reflected in hormone excretion. The results are summarized in figure 5 and table 4.

Two of these women (O. W. S. and L. D. Y.) have also been studied when not pregnant. It is interesting to note (tables 2 and 4) that their mean values creatinine excretion as well as their coefficients

variation and maximum deviations from the mean were the same in the pregnant as in the nonpregnant state. Considering the tremendous hormone changes that take place during pregnancy, this observation argues against any direct effect of the female sex hormones upon creatinine excretion.

### *Creatinine Excretion During Labor*

Urinary estrogens, pregnanediol and creatinine have been measured in repeated specimens from 4 women during labor. An indwelling catheter was employed in 2

It is impossible to explain the significance of this finding, especially since neither the creatinine content of the blood was followed nor was urinary creatinine measured. However, it is sufficiently striking to indicate that some marked change in creatinine metabolism accompanies labor and delivery. There is no experimental indication that muscular exercise would result in a decrease in urinary creatinine, in fact, there is convincing evidence that muscular exercise temporarily increases the rate of creatinine excretion (21, 22). We would consider the striking drop

TABLE 6A CREATININE EXCRETION IN 9 WOMEN WHO HAD OR DEVELOPED PREECLAMPSIA DURING PERIOD OF STUDY (to 6 of these sex hormones were administered). Comparison of values during normal, pathological and experimental conditions

| Subject | Clinically Normal |            |                         | Showing Clinical Manifestations of Preeclampsia |            |                        |                               |                |            |                 |
|---------|-------------------|------------|-------------------------|---|------------|------------------------|-------------------------------|----------------|------------|-----------------|
|         | Weeks pregnant    | No of spec | Range of values         | No hormones administered                        |            |                        | During hormone administration |                |            |                 |
|         |                   |            |                         | Weeks pregnant                                  | No of spec | Range of values        | Hormonal R <sup>1</sup>       | Weeks pregnant | No of spec | Range of values |
| MP      | 10 to 36          | 5          | gm /24 hr.<br>0.97-1.06 | 36 to 38  | 3          | gm /24 hr<br>0.87-1.14 |                               |                |            | gm /24 hr       |
| WH      | 25 and 28         | 2          | 1.29-1.43               | 34 and 36                                       | 2          | 1.31-1.41              |                               |                |            |                 |
| RW      | 31 and 34         | 2          | 0.94-1.00               | 34½   | 1          | 1.00                   |                               |                |            |                 |
| GK      | 22 to 31          | 6          | 0.91-1.05               |   |            |                        | EB (10)+T (25)                | 32 to 37       | 8          | 0.83-1.09       |
| ML      | 26 to 32          | 5          | 1.05-1.20               | 32 to 33  | 4          | 0.88-1.09              | PG (5 cc)                     | 33 to 35       | 9          | 0.88-1.27       |
| JK      | 27 and 28         | 2          | 1.33-1.42               |   |            |                        | Stilbestrol (40)              | 29 to 30       | 3          | 1.33-1.44       |
|         |                   |            |                         |   |            |                        | EB (10)+P (20)                | 31 to 37       | 4          | 1.37-1.45       |
| RM      |                   |            |                         | 36 to 37  | 3          | 0.94-1.23              | EB (10)+P (50)                | 37 to 39       | 4          | 0.93-1.01       |
| HH      |                   |            |                         | 34 to 35  | 3          | 0.92-1.12              | EB (10)+P (50)                | 35 to 37       | 5          | 0.94-1.05       |
| V.M     |                   |            |                         | 34 to 36  | 6          | 1.26-1.45              | PG (5 cc)                     | 36 to 37       | 4          | 1.25-1.53       |

<sup>1</sup> EB, estradiol benzoate, T, testosterone propionate, P, progesterone. Figures in parentheses, mg. injected daily. PG, Pituitary gonadotropic factor (Prephsyn, Chappel), 5 cc (marked 125 u) given daily.

of them, collections from the other 2 were personally supervised by the writer. The results on urinary estrogens and pregnanediol indicated that labor contractions in all, in 1 of whom labor was induced, were accompanied by a progressive and rapid decrease in hormone excretion together with a sudden marked increase in the rate of sex steroid destruction (11). The creatinine values (table 5), based on 2 to 10 hour specimens, are all expressed in terms of 24-hour excretion for the sake of comparison. There was in each case a 34 to 54% decrease in the rate of creatinine excretion between the onset of labor and delivery, this being the most marked change in creatinine output that we have encountered in our observations upon pregnant and non-pregnant women.

during labor as similar to the observations reported above at the time of menstruation and due to similar though as yet undetermined causes. The same hormonal changes which characterize menstruation (6) pertain, on a larger scale, during labor and delivery (11). It seems likely that the circulatory changes, vasoconstriction and increased capillary permeability with concomitant water and salt retention, which we know are associated with the menstrual phenomenon and with changes in sex hormone metabolism, are also associated with labor and delivery and might well affect creatine and creatinine metabolism.

### *Creatinine Excretion in Women With Preeclampsia*

*Effect of hormone administration.* The data on 9 preeclamptics, 6 of whom were followed prior to the

onset of toxic manifestations and to 6 of whom hormones were administered, are summarized in tables 6, A and B. In all of the first 6 individuals, hormone studies prior to the onset of clinical abnormalities gave evidence of an abnormal rise in serum chorionic gonadotropin and a gradual decrease, rather than the normal increase, in serum estrogen and the levels of estrogens and pregnanediol in the urine. In each case, toxic manifestations were accompanied by a marked increase in the rate of steroid destruction (8). There was no indication, however, that any consistent change in creatinine excretion either preceded or accompanied the hormonal and clinical abnormality. There was also no apparent correlation between the fluctuations in creatinine excretion and either the clinical or endocrine changes which followed injections. In table 6, B, the creatinine data on the 8 preëclamptic patients from whom a total of 4 or more specimens were collected are summarized. It is ap-

flowing, unlike normal menstruation, being gradual rather than sudden in its onset. Furthermore, in those patients in whom hormone administration appeared to shift the hormonal and clinical abnormality in the direction of normal, the effect was by no means spectacular, but took place gradually over a 6-day or longer interval of daily injections. It is entirely possible that any influence upon creatine and creatinine metabolism would depend upon the rapidity with which the causative metabolic shifts take place.

*Creatinine Content of Urine as a Gauge of  
Accuracy of Collections and Basis for  
Calculated 24-Hour Volumes*

The data presented demonstrate, as has been noted by others, (22, 23, 24) that the 24-hour excretion of creatinine by any individual is only relatively constant. The largest coefficient of variation observed in any woman of our series has been 12.5% and the

TABLE 6B. SUMMARY OF DATA OF TABLE 6A, DEMONSTRATING THAT CREATININE EXCRETION IN PREËCLAMPTIC WOMEN TO WHOM SEX HORMONES ARE ADMINISTERED IS AS CONSTANT AS IN NORMAL PREGNANCY (CF. TABLE 4)

| Subject           | Stage of Pregnancy | No. of Specimens | Range of Values   | Mean Value and Std. Dev. | Coef. of Var. | Maximum Deviation |          |
|-------------------|--------------------|------------------|-------------------|--------------------------|---------------|-------------------|----------|
|                   | <i>weeks</i>       |                  | <i>gm./24 hr.</i> | <i>gm./24 hr.</i>        | <i>%</i>      | <i>gm.</i>        | <i>%</i> |
| M.O.              | 10 to 38           | 8                | 0.87-1.14         | 1.03±0.08                | 7.7           | 0.16              | 15.5     |
| W.H.              | 25 to 36           | 4                | 1.29-1.43         | 1.36±0.07                | 5.1           | 0.07              | 5.1      |
| G.K.              | 22 to 37           | 14               | 0.83-1.09         | 0.99±0.09                | 9.1           | 0.16              | 16.2     |
| M.L. <sup>1</sup> | 26 to 35           | 18               | 0.88-1.27         | 1.05±0.10                | 9.5           | 0.22              | 20.9     |
| J.K.              | 27 to 37           | 9                | 1.33-1.46         | 1.39±0.05                | 3.6           | 0.07              | 5.1      |
| R.M.              | 36 to 39           | 7                | 0.93-1.23         | 1.05±0.11                | 10.5          | 0.18              | 17.1     |
| H.H.              | 34 to 37           | 8                | 0.92-1.12         | 1.00±0.07                | 7.0           | 0.08              | 8.0      |
| V.M. <sup>1</sup> | 34 to 37           | 10               | 1.25-1.53         | 1.37±0.09                | 6.6           | 0.16              | 11.7     |

<sup>1</sup> Based on analyses of 12-hr. specimens collected from P.M. to A.M.

parent that the coefficients of variation and the maximum deviations from the mean values in these women, to 6 of whom large daily doses of hormones were given, are no greater than those encountered in normally pregnant women (table 4).

The hormonal changes which precede and accompany the onset of preëclampsia are entirely similar to those which occur after the onset of labor and which characterize the menstrual phenomenon. In the latter two situations we have evidence that creatine and creatinine metabolism are affected, whereas the data of tables 6, A and B, indicate that a similar situation in preëclampsia does not affect creatinine excretion. This may be accountable to the fact that the changes during labor and at the onset of menstruation take place over a comparatively short interval, whereas in the preëclamptic individual similar changes are going on over a period of weeks before the toxemic condition becomes clinically apparent. In the above case of functional uterine bleeding (B. V. A.) the same type of estrogen degradation pertained whether the patient was in a bleeding or an amenorrheic stage, the

greatest maximum deviation from the mean 25%. In general, both values have been considerably lower than these figures. Various physiological, pathological and experimental conditions do not appear to affect the range of values for any individual, the only exception to this statement being the marked decrease in the rate of creatinine excretion during labor. When repeated specimens from an individual are being analyzed, therefore, the finding of a 24-hour creatinine value more than 25% higher or lower than the average for that individual would seem to warrant the assumption (unless the patient is in labor) that an error in collection has been made. In fact, any value under 0.80 gm. in 24 hours is open to suspicion.

In table 7 we have analyzed representative data demonstrating the gross errors that may be expected under ordinary hospital conditions. The results on B. V. A. are particularly revealing, since the 10 hospital collections may be compared with 14 other specimens from this same individual which we know were reliable (see table 3), 5 while she was on con-

stant drainage and 9 which she collected herself at home. Despite the fact that special nurses were assigned to this case for the sake of obtaining accurate collections of urine, the coefficient of variation and the maximum deviation from the mean on the 10 hospital specimens were both nearly 3 times as high as those on the 14 reliable 24 hour volumes. Actually, the error was even greater than would appear from the figures, since we may assume that the true mean value for the hospital voidings was about 0.95 gm of creatinine in 24 hours rather than 0.74 gm. This would give a coefficient of variation of 28% and a maximum deviation of 48%. In other words, if we had not performed creatinine determinations and had accepted the volumes received as true 24 hour col-

available, we have had to assume a creatinine coefficient for the individual being studied and recalculate, on the basis of this assumed figure, a corrected 24 hour volume for all specimens according to their creatinine content. Although this procedure is open to criticism, it at least gives comparable day to day values of hormone excretion and is certainly preferable to accepting volumes as received from any ordinary hospital ward.

Even when a patient has private nursing care, errors appear to be unavoidable and for this reason some check on the accuracy of every 24-hour volume is absolutely essential when quantitative urinary studies are being conducted. We have found that individual patients are for the most part very consci-

TABLE 7 CREATININE EXCRETION BASED ON 24 HOUR VOLUMES AS RECEIVED FROM HOSPITALIZED PATIENTS, DEMONSTRATING THE GROSS ERRORS INTRODUCED THROUGH INACCURATE COLLECTIONS  
(Compare with tables 2, 3, 4 and 6B)

| Subject          | Clinical Notes               | No of Specimens | Range of Values         | Mean Value and Std. Dev.  | Coef of Var. | Maximum Deviation |           |
|------------------|------------------------------|-----------------|-------------------------|---------------------------|--------------|-------------------|-----------|
| BVA <sup>1</sup> | Metrorrhagia<br>Preeclampsia | 10              | gm / 24 hr<br>0.49-0.98 | gm / 24 hr<br>0.74 ± 0.16 | %<br>21.6    | gm<br>0.25        | %<br>33.8 |
| AD <sup>2</sup>  | 33-34 wk                     | 8               | 0.30-0.98               | 0.65 ± 0.25               | 38.4         | 0.33              | 51.0      |
| JE <sup>2</sup>  | 33-38 wk                     | 9               | 0.30-0.92               | 0.66 ± 0.20               | 30.3         | 0.36              | 55.0      |
| LS <sup>2</sup>  | 30-32 wk                     | 10              | 0.39-1.32               | 0.80 ± 0.32               | 40.0         | 0.52              | 65.0      |
| MB <sup>2</sup>  | 30-34 wk                     | 9               | 0.40-1.20               | 0.79 ± 0.34               | 43.0         | 0.41              | 52.0      |
| AG <sup>2</sup>  | 36-38 wk                     | 11              | 0.13-1.60               | 0.90 ± 0.43               | 47.8         | 0.77              | 86.0      |
| RC <sup>2</sup>  | 35-37 wk                     | 9               | 0.45-1.55               | 1.03 ± 0.31               | 30.1         | 0.58              | 56.0      |

<sup>1</sup> Patient under private nursing care, written orders given for 24 hour urine collection

<sup>2</sup> Patients on ward service, written orders given for 24 hour urine collections

lections, we would have introduced into our studies of hormone excretion possible errors 4 times as great, according to the reliable data on this patient (table 3), as those that may have resulted from recalculating 24 hour volumes on the basis of creatinine content.

The other 6 patients in table 7 were followed while in the toxemic ward of a large obstetrical hospital. Written orders were given and directions posted for the accurate collection of 24 hour volumes. The maximum deviations from the mean vary between 51 and 86% and the coefficients of variation lie between 30 and 48%. A comparison of these figures with those in tables 2, 3, 4 and 6, B demonstrate the magnitude of the errors that may be introduced by inaccurate collections. Here again these figures, must underestimate the true errors, since the low mean values on these patients indicate that most of the mistakes were due to loss of urine and that the average daily excretion of creatinine for each individual was probably closer to the highest figure in the range of values. On this basis the maximum deviations would be 80 to 115% as compared with 5 to 25% in the reliable collections from pregnant women. In such cases, where no known reliable collections have been

enthusiastic about collections provided they are given full and careful instructions. Whenever possible, we have had patients supervise their own collections while in hospitals.

We have found hospital specimens more accurate if only 12 hour volumes from 7 P.M. to 7 A.M. are followed, since during these hours there are fewer voidings, less general activity in the ward and fewer nurses on duty. (In studying estrogen and pregnanediol excretion, this is possible only in pregnant women, since 24 to 72 hour volumes are required from nonpregnant patients in order to get enough material for accurate assay.) Comparison of the day and night excretion of creatinine in a number of our patients has shown that, although some women excrete more creatinine at night than during the 12-hour day period and others excrete less, 12 hour values are as constant as 24 hour amounts, provided collections on a given individual always cover the same 12 hour interval. This observation has been reported by others (22, 23, 25). Bachman (26) has recently shown that the rate of pregnanediol excretion and of the 17 ketosteroids does not vary from day to night and is not affected by the volume of urine.

Our own studies (unpublished data) confirm this observation for pregnanediol and show that the same constancy in rate of excretion applies to the estrogens. It would appear, therefore, that the analysis of 12-hour rather than 24-hour volumes is a perfectly reliable procedure. Under no conditions, however, have we ever felt justified in omitting creatinine determinations as a check on the accuracy of hospital collections.

#### SUMMARY AND CONCLUSIONS

The 24-hour excretion of preformed creatinine has been measured in 6 menstruating women (140 determinations during 14 cycles); in 5 women with gynecological disorders to 4 of whom estrogenic, progestational or gonadotropic hormones were administered (56 determinations); in 1 woman before and during the cycle of conception and during the first 2 months of a pregnancy complicated by threatened abortion (27 determinations); in 10 women during the course of normal pregnancy (80 determinations); in 4 women during labor (19 determinations); and in 9 women who developed preëclampsia, to 6 of whom large amounts of estrogen, progestin, testosterone or pituitary gonadotropic hormone were administered (81 determinations). Urinary creatine has been measured in 4 of the menstruating women (113 determinations during 11 cycles). Urinary estrogens (either total or separated) were also measured in all specimens, the gonadotropic potency of the urine in many and urinary pregnanediol in those from pregnant women.

In menstruating women there was evidence that, though ovarian secretion did not directly affect creatine and creatinine excretion, a definite change in creatine and creatinine metabolism was associated with the menstrual phenomenon itself.

Neither gynecological disorders nor the administration of hormones to nonpregnant women in amounts sufficient to cause physiological changes and markedly to affect hormone excretion, appeared to influence the creatinine output.

The only consistent or significant change in urinary creatinine in normal pregnancy was found during the course of labor, when a striking drop in the rate of its excretion was encountered.

Creatinine excretion was not demonstrably affected by the development of preëclampsia despite the accompanying marked changes in hormone metabolism, or by the large amounts of sex hormones administered to patients with the disease.

From the data presented we are led to believe that any effect of female sex hormones upon creatine and creatinine excretion may depend upon rapid shifts in sex steroid metabolism and accompanying rapid changes in vascular supply and in water and salt balance, rather than directly upon the amounts and kinds of hormones secreted or administered.

Under all of the conditions investigated, except during labor, creatinine determinations were found to provide a satisfactory gauge of the accuracy of 24-hour collections. Any value of less than 0.8 gm. in 24 hours may be considered open to suspicion and the finding of a 24-hour creatinine value more than 25% higher or lower than the average for a given individual appears to warrant the assumption that an error in collection has been made.

The most dependable collections are made by carefully instructed patients, either at home or when supervising their own hospital collections. Ward specimens are extremely unreliable and even with special nursing care gross errors appear to be unavoidable. The collection of 12-hour rather than 24-hour amounts reduces these errors. Recalculation of the 24-hour volumes of specimens in which gross errors are apparent, on the basis of the creatinine concentration and an assumed or known average 24-hour creatinine output for a given individual, greatly reduces the inaccuracy of results. Some check on the accuracy of collections is an essential part of any quantitative urine analysis.

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# Creatine Retention Capacity of Boys in Relation to Androgen Function<sup>1 2</sup>

## [Androgens and Creatine Metabolism]

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IT IS KNOWN that prepuberal boys and girls and adult women exhibit a creatinuria though the adult male does not. Also that the tolerance for exogenous creatine is much less in the former group than in the adult male. The difference in tolerance between the sexes is, apparently, not due to a difference in sex, per se, since some muscular women exhibit a marked capacity to retain exogenous creatine (1).

It is believed that a poor creatine tolerance occurs until about the age of 13 years and parallels the physiological creatinuria of adolescence (2).

Castrates, eunuchoids, aged humans and those exhibiting hypogonadism also show impaired creatine retention. This interest is focused on the relation of hormones to the metabolism of creatine. Remen (3) found a creatinuria in elderly men (70-90 years), one eunuch and one castrate. These behaved like infants and children in that they excreted most of the injected creatine. Thus he concludes the male gonad has a definite effect on creatine excretion.

Sutton (4) reports a retention of exogenous creatine in prostates (52-68 years) and nonprostates (54-77 years) comparable to that of young men (24-37 years). This retention of exogenous creatine was not increased in normal young males or elderly prostates by administering 200 mg of testosterone propionate in divided doses.

Schittenhelm and Buhler (5) found a spontaneous creatinuria in diseases of the pituitary, thyroid and gonads. Patients with gonad insufficiencies excrete more exogenous creatine than do patients with other conditions. Thus the gonad has important function in that it can prevent creatinuria and when gonadal function is lost, creatinuria occurs.

That there is a definite relation between the hormones and the metabolism of creatine has been shown

by many recent workers. While much of the experimental work points to an increased creatine tolerance and a reduction of creatinuria brought about by the administration of certain hormones, the opposite has also been reported.

Kun and Peczenik (6) have induced a creatinuria in rats castrated postpuberally which they were able to suppress by administration of urinary androgen.

Coffman and Koch (7) found the creatinuria of the control period following castration to be small. Exogenous creatine, however, produced an intense creatinuria which could be suppressed by injections of testosterone propionate.

Kenyon et al (8) reduced the creatine excretion in a eunuchoid, intensified by exogenous creatine, by the daily administration of testosterone propionate.

Koven and Beard (9) and Pizzolito and Beard (10) observed a creatinuria in rats following castration. They also report a creatinuria following injection of anterior pituitary extracts, estrogen, testosterone, cortin and saline and water.

In relation to the young age group Buadze (11) claimed that male hormone stops the creatinuria of childhood while female hormone increases it. Buhler (12) reported that neither estrogen nor androgen had any effect in increasing creatine tolerance in childhood.

Jailer (13) was able to abolish the creatinuria of young male monkeys and increase their capacity to retain exogenous creatine by the administration of testosterone propionate. Castration in mature monkeys resulted in an increased creatinuria and impaired creatine retention. The injection of testosterone propionate abolished the creatinuria of castration and restored the capacity to retain creatine. Estradiol benzoate had no effect on creatine excretion. None of the procedures produced any effect on creatinine excretion.

### EXPERIMENTAL PROCEDURE

The experiments here reported are concerned with the relation of chorionic gonadotropic hormone<sup>3</sup> and

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<sup>2</sup> Aided by a grant from the Rockefeller Foundation administered by Dr Philip E Smith.

<sup>3</sup> Presented in partial fulfillment of the degree of Doctor of Medical Science, College of Physicians and Surgeons, Columbia University, New York City.



TABLE 1. EFFECT OF CHORIONIC GONADOTROPIN ON CREATINE RETENTION IN BOYS

| Patient Age  | Control Period |                         |                                 | After Gonadotropin Injection |            |                         |                                 |
|--------------|----------------|-------------------------|---------------------------------|------------------------------|------------|-------------------------|---------------------------------|
|              | Creatinine     | Creatinine <sup>1</sup> | C.R.T. <sup>2</sup> (excretion) | R.U. administered            | Creatinine | Creatinine <sup>1</sup> | C.R.T. <sup>2</sup> (excretion) |
| R.R., 5 yr.  | mg. 353        | mg. 287                 | % 69                            | 5500                         | mg. 349    | mg. 182                 | % 65<br>83                      |
| G.B., 7 yr.  | 436            | 129                     | 77<br>99                        | 8800                         | 536        | 98                      | 82<br>91                        |
| S.Z., 8 yr.  | 455            | 74                      | 55<br>75                        | 2500                         | 487        | 220                     | 73<br>84                        |
| K.J., 8 yr.  | 365            | 48                      | 51<br>66                        | 8500                         | 776        | 154                     | 96<br>100                       |
| G.F., 9 yr.  | 505            | 214                     | 61<br>91                        | 6050                         | 621        | 66                      | 65<br>96                        |
| J.C., 10 yr. | 433            | 143                     | 67<br>86                        | 4200 <sup>+</sup>            | 533        | 337                     | 65<br>89                        |
| C.L., 10 yr. | 523            | 285                     | 44<br>98                        | 6500                         | 587        | 201                     | 81<br>100                       |
| D.K., 10 yr. | 566            | 101                     | 43<br>56                        | 3000                         | 864        | 116                     | 41<br>52                        |
| L.T., 11 yr. | 877            | 131                     | 36<br>38                        | 5450                         | 819        | 29                      | 26<br>28                        |
| A.P., 14 yr. | 646            | 194                     | 68<br>—                         | 1800                         | 679        | 250                     | 65<br>79                        |

<sup>1</sup> As creatinine.<sup>2</sup> Creatine retention test.

ndrogenic hormone<sup>4</sup> to creatine metabolism in young males. Eighteen subjects were used, with each serving as his own control. These patients were kept on a meat-free diet the day preceding, during, and the day following that of creatine feeding. Twenty-four hour samples of urine were analyzed for creatinine and creatine following the methods of Folin (14) and the modification of Benedict and Myers (15) respectively. The urines were tested for sugar and acetone at various intervals since these interfere with the Jaffe reaction.

The creatinine values were expressed in milligrams and the creatine in milligrams of creatinine. Five consecutive 24-hour samples were used. Two grams of creatine hydrate were given on the morning of the 4th day. The 5th sample was collected in order to have a determination of the excretion of exogenous creatine in 48 hours.

Following this control series the patients were given a course of gonadotropic factor intramuscularly (200 R.U. 3 times weekly) and the above tests repeated.

Then following a rest period, a course of testosterone propionate (25 mg. 3 times weekly intramuscularly) was given and the tests again repeated.

*Creatine excretion in immature males.* Immature males show a creatinuria of varying degree. When

given creatine retention tests a high percentage of the exogenous creatine is excreted in the urine. In the above tests the average excretion in 24 hours during the control series was 67% of the ingested creatine. This was the average of an actual variation ranging from 43 to 84%. Fifty-six to 99% of the creatine was excreted in the 48-hour period following the ingestion of 2 gm. of creatine hydrate.

Following the injection of gonadotropin as illustrated in table 1 the average excretion (omitting case L. T.) in 24 hours was 70%. The actual excretion varied from 41 to 96%. In the case of case L. T. the excretion was low both during the control period and following gonadotropic therapy with no appreciable change being produced by the hormone.

Similarly, following the administration of androgen (table 2) the excretion of exogenous creatine was high. Again omitting case L. T. and also case A. G. the average excretion in 24 hours was 83%. The actual excretion varied from 69 to 100%.

With the exception of case A. G. it would seem that the injection of gonadotropic or androgenic hormones, in the doses illustrated produces no increase in creatine retention and, in many cases, there is an actual decrease, i. e., an increase in the excretion of exogenous creatine.

Case A. G., who showed an increased retention of exogenous creatine following androgen therapy, was an obese 9-year-old male of the Fröhlich type whose B.M.R. was -24%. The left testicle was normally placed in the scrotum, the right was palpable in the upper canal and atrophic. Secondary sexual changes were present in this boy (rather marked growth of suprapubic hair and palpable prostatic tissue) previ-

TABLE 2. EFFECT OF TESTOSTERONE PROPIONATE ON CREATINE RETENTION IN BOYS

| Patient, Age | Control Period |                         |                                 | After Androgen Injection |            |                         |                                 |
|--------------|----------------|-------------------------|---------------------------------|--------------------------|------------|-------------------------|---------------------------------|
|              | Creatinine     | Creatinine <sup>1</sup> | C.R.T. <sup>2</sup> (excretion) | Amount                   | Creatinine | Creatinine <sup>1</sup> | C.R.T. <sup>2</sup> (excretion) |
| G.B., 7 yr.  | mg. 436        | mg. 129                 | % 77<br>99                      | mg. 350                  | mg. 472    | mg. 156                 | % 83<br>100                     |
| N.R., 8 yr.  | 834            | 577                     | 65<br>100                       | 450                      | 753        | 577                     | 100                             |
| G.F., 9 yr.  | 505            | 214                     | 61<br>91                        | 425                      | 539        | 357                     | 93<br>100                       |
| A.G., 9 yr.  | 838            | 83                      | 62<br>67                        | 300                      | 889        | 83                      | 27<br>33                        |
| S.B., 10 yr. | 794            | 113                     | 61<br>90                        | 350                      | 868        | 80                      | 71<br>80                        |
| L.T., 11 yr. | 877            | 130                     | 36<br>38                        | 325                      | 849        | 115                     | 34<br>42                        |
| A.P., 14 yr. | 646            | 194                     | 68<br>—                         | 585                      | 794        | 179                     | 69<br>100                       |
| J.K., 15 yr. | 1012           | 322                     | 84<br>94                        | 300                      | 1001       | 456                     | 83<br>100                       |

<sup>1</sup> As creatine.<sup>2</sup> Creatine retention test.

<sup>3</sup> Chorionic gonadotropin (Follutein) supplied by E. R. Squibb & Sons, New Brunswick, N. J.

<sup>4</sup> Testosterone propionate (Perandren) supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

ous to androgen therapy This boy was not given a course of gonadotropin

Case L T, who showed an increased retention or retention paralleling that of a normal adult, was a tall asthenic 11 year old male The left testicle was normally placed in the scrotum, the right was not palpable in the scrotum or inguinal canal This boy also presented marked secondary sexual changes before treatment was instituted which were perhaps augmented by androgen therapy.

#### DISCUSSION

From the results here presented it can be concluded that, in the doses given, the creatinuria of young males cannot be abolished or even decreased by the administration of gonadotropic or androgenic hormones Normally these cases do not retain a great deal of the ingested creatine, excreting from 50 to 100% Following injection of chorionic gonadotropin or testosterone propionate, as illustrated, this retention capacity is not enhanced and indeed, may even be less

In consideration of case A G where the opposite was found to be true one cannot be sure that the results were not purely a coincidental finding These changes may have been occurring normally at this time and were perhaps augmented by the hormone therapy

Explanations of the creatinuria of childhood are many and varied The ingestion of protein appears to influence elimination of creatine Yet there is no direct relation between the amount of protein ingested and the amount of creatine excreted The relationship differs with different children but is fairly constant for a given child, i.e., one child may excrete more creatine than another though its protein intake be less (16)

It has been suggested that creatine is a product of amino acid catabolism and a certain amount is necessary for physiological processes In children with a high protein intake in proportion to body weight more is formed than is needed and the excess is excreted A slightly different view has been expressed by Hunter (1) "Creatine is the end product in the catabolism of certain precursors in the protein molecule just as urea is of others If these precursors are present in excess relative to the demands for protein synthesis they will be transformed to creatine and partly excreted"

Creatinine is believed to be a normal nitrogenous end product of muscle metabolism The amount excreted gradually increases with age and is not related to protein intake

Nitzescu and Gantzea (17) conclude that creatinuria of childhood is due to the presence of the growth hormone In their opinion the growth hormone increases creatinuria, diminishes tolerance to administered creatine, and inhibits the effect of the male hormone on creatinuria

In considering Buhler's conclusion that androgen has no effect in increasing creatine tolerance in childhood, one must remember that only one dose of an androgenic factor (proviron) was given and that orally

The statement of Buadze (11) that "male hormone stops the creatinuria of childhood" is not confirmed by the results found in this work

Jailer (13) states that "the injection of testosterone propionate causes an abolition of creatinuria in immature monkeys and increases their capacity to retain creatine" Only 2 of the monkeys are stated to be definitely immature with inguinal testes The estimation of age in these cases is a comparative estimate based on the weight of the animal Thus the possibility of their being adolescent rather than immature monkeys must be considered (Jailer, personal communication). Or, as in the case of some human individuals (case A G, age 9 years) secondary changes may have begun at an earlier age and thus the quoted result obtained

#### SUMMARY AND CONCLUSIONS

Immature males excrete creatine and show impaired retention of exogenous creatine

Injection of gonadotropin as illustrated in this work produces no significant change in creatinuria and does not increase the capacity to retain creatine

Injection of androgen as illustrated produces no change in creatinuria nor does it increase the capacity to retain creatine

None of the procedures produced any significant effect on the level of creatinine excretion

I wish to express my appreciation and gratitude to Dr. Earl T. Engle, Department of Anatomy, College of Physicians and Surgeons, Columbia University, for his valuable aid and interest

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# Effects of Testosterone Propionate and Stilbestrol on the Mammary Gland Postpartum

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THERE HAVE BEEN SEVERAL REPORTS on the value of testosterone propionate and stilbestrol in combating the pain of breast engorgement and in inhibiting lactation following delivery (1-6). The results reported have, in the main, been favorable and if they are confirmed by a sufficient number of investigators, these materials may be safely added to the obstetrician's armamentarium.

The opportunity was presented for observation of some effects of testosterone propionate on the mammary gland and its secretion following delivery. The study was made on 139 patients. Of these, 55 were used as controls and 84 were given testosterone propionate or stilbestrol. There were 15 patients in whom it was necessary to stop lactation; of these, 7 received testosterone propionate by deep hypodermic injections and 8 were given stilbestrol orally. Sixty-nine patients received testosterone propionate.

The procedure employed for combating the pain of breast engorgement in the control group consisted of the application of ice packs with tight binders to the breasts, the limitation of fluids and the use of codeine. For the patients receiving testosterone propionate no additional treatment was given. The oral dosage of testosterone varied from 20 to 30 mg. as compared to the 10 to 15 mg. when given by deep hypodermic injection. At the first subjective sign of engorgement, the initial dose of testosterone propionate was given, 10 mg. orally or 5 mg. by deep hypodermic injection. This was followed in 6 hours by a second and, if pain persisted, a third was given.

The evaluation of pain was made as follows: no pain, slight pain and much pain. This is, of course, entirely subjective and dependent upon the emotional make-up of the patient. However, since pain was the only thing to combat, we considered the patient's complaint as a reliable gauge. We listed those pa-

## [[Mammary Engorgement]]

tients as having much pain who would have received codeine, tight binders, ice packs and limitation of fluids, for relief. These were the only patients who received a third dose of testosterone propionate.

Table 1 shows the effect of testosterone propionate

TABLE 1. RESULTS OF THERAPY WITH TESTOSTERONE PROPIONATE IN CASES OF BREAST ENGORGEMENT

| Engorgement Onset                          | Control Group<br>55 Patients     |    | Treated group<br>69 Patients     |    |
|--|----------------------------------|----|----------------------------------|----|
| Time of:<br>Average<br>Shortest<br>Longest | 61 hours<br>40 hours<br>83 hours |    | 57 hours<br>30 hours<br>97 hours |    |
|  | No.                              | %  | No.                              | %  |
| No pain                                    | 31                               | 57 | 30                               | 44 |
| Slight pain                                | 11                               | 19 | 17                               | 24 |
| Much pain                                  | 13                               | 24 | 22                               | 32 |

on painful engorgement as compared with the control group. Approximately 57% of the patients in the control group had no pain; 44% of those treated with testosterone propionate had pain. About  $\frac{1}{4}$  of the control group had much pain as compared to  $\frac{1}{3}$  of the treated patients. The time of onset of engorgement for the control group was 61 hours and for the treated group 57 hours post partum.

Table 2 shows the comparison between the control and treated patients regarding the average time of onset of lactation and the average amount of milk obtained. Of the control group, 6% produced milk on the 2nd day and 38% on the 3rd day so that a total of 44% were lactating by the end of the 3rd day. Of the 69 patients receiving testosterone, none had milk by the end of the 2nd day and only 8% were lactating by the end of the 3rd day. By the 5th day all patients of both groups were lactating and the average amount in each group was essentially the same.

Of the 55 patients in the control group, 5 had to

give up nursing because of lack of milk. However, 3 of these patients had not nursed their previous babies for the same reason. The remaining 2 patients (one primipara and one multipara) make up 4% of the total. Of the 69 patients receiving testosterone propionate, 8, or 11%, had to stop nursing due to insufficient milk. One of this latter group had not nursed her last baby for the same reason; the remaining 7 patients (6 primiparae and 1 multipara) constitute 10% of the group.

There were 15 patients who were given hormone products to prevent and/or discontinue lactation. Of these, 8 patients had stillbirths, 3 refused to nurse

TABLE 2

| Days Post partum | Amount of Milk Produced |     |                     |     |
|------------------|-------------------------|-----|---------------------|-----|
|                  | Control, 55 Patients    |     | Treated 69 Patients |     |
|                  | Av amount, oz           | %   | Av amount, oz       | %   |
| 2                | 2 5                     | 6   | 0                   | 0   |
| 3                | 2 5                     | 44  | 3                   | 8   |
| 4                | 5                       | 94  | 4                   | 91  |
| 5                | 7 5                     | 100 | 7                   | 100 |
| 6                | 9 5                     |     | 9                   |     |
| 7                | 11                      |     | 11                  |     |
| 8                | 9                       |     | 11                  |     |
| 9                | 11                      |     | 12 5                |     |

the infants, 2 were unmarried women, 1 patient's baby died at 3 months of age and 1 patient developed mastitis on the 10th day post partum. Seven of these patients were given deep hypodermic injections of testosterone propionate. The total dosage ranged from 50 to 100 mg in 25 mg doses at 24 hour intervals. Of these 7 patients, 6 received the initial dose at the onset of engorgement. The 7th patient who had nursed her baby for 3 months was given 50 mg in 2 days, lactation stopped by the 3rd day. Careful and frequent inspection revealed soft and non lactating breasts in all cases by the end of the 5th day after treatment was instituted.

The remaining 8 patients of this group were treated with diethyl stilbestrol. Of these, 4 were given a total of 8 to 12 mg starting on the 2nd day after delivery, a 1 mg dose being given 3 times daily. They all had soft, non lactating breasts within 4 days. Three patients were given a total of 4 to 8 mg each starting on the 2nd day, 1 mg being given twice daily. These 3 had in addition to the medication the application of tight binders and ice packs to their breasts. In these 3 cases the breasts were soft and non lactating within 3 days after treatment was started. The remaining patient who had received no treatment developed mastitis on the 10th day post partum. She had been lactating for about 7 days. Therapy con-

sisted of 1 mg of stilbestrol 3 times daily for 3 days and ice bags to the involved tissue. The breasts were soft and non lactating by the 3rd day of treatment and the affected area rapidly healed.

In the control group of 55 patients, 4 developed mastitis. Of these, 2 progressed to abscess formation necessitating incision and drainage. There were no complications in the patients receiving testosterone propionate.

#### DISCUSSION

The action of these hormone products is generally considered to be a suppression of the mammary secretagogue produced by the pituitary gland (7-10). There is no evidence that the use of testosterone propionate or of stilbestrol in small doses for a short time is injurious to the patient. However, there may be temporary suppression of ovarian activity. These hormone products were noted to have no apparent effect on the involution of the uterus, the amount of lochia and the development of afterpains. There were no unpleasant after effects, nor did we note any local reactions in the areas of injection.

From this study testosterone propionate offers no apparent advantage over the routine treatments employed at present for the control of pain in puerperal breast engorgement. If any effect of this product can be noted with the dosage used, it is one of delay of the onset of lactation without a delay or even with an earlier appearance of engorgement. The ultimate effect of testosterone propionate is probably one of permanently inhibiting lactation as is evidenced by a 10% failure in ability to nurse as compared with 4% in the control group. It is presumptuous to make positive statements on so small a series of cases but if these findings are later confirmed, the use of testosterone propionate for such minor puerperal difficulties as painful breast engorgement should be discouraged.

In patients in whom it is advantageous to subdue or discontinue lactation, testosterone propionate and stilbestrol are equally satisfactory. At the present time, the high cost of the former product plus the fact that it is apparently more effective when used by the parenteral route makes stilbestrol appear to be the choice of available single procedures. This compound used with tight binders and ice packs to the breasts bids fair to become an ideal method for the suppression of lactation.

#### SUMMARY

A study of 124 patients was made to determine value of testosterone propionate in the prevention of the pain of breast engorgement in the puerperium. The results showed this compound to be of little or no value for this purpose and of some disadvantage

since it caused a delay and discontinuance of lactation.

Testosterone and diethylstilbestrol are useful in preventing or discontinuing lactation.

A combination of diethylstilbestrol with tight binders and ice packs appears to be ideal for suppression of lactation.

Our appreciation is extended to Ciba Products Company, Incorporated, Summit, N. J., for their generous supply of Metandren and Perandren. Also the Eli Lilly and Company, Indianapolis, Indiana, for their generous supply of diethylstilbestrol.

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# Stilbestrol Monomethyl Ether<sup>1</sup>

## Report on Its Clinical Use

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## [Menopausal Syndrome]

INVESTIGATIONS, principally by Dodds and his co-workers, have shown that estrogenic activity is not confined to the naturally occurring substances of steroid structure (1). Over a hundred synthetic substances have been shown to be estrogenic in varying degree. Of these materials by far the most important is stilbestrol. The structural relationship of this synthetic compound to the naturally occurring estradiol is apparent on consideration of the two formulae (fig 1, 2). Although the over-all dimensions and general architecture of the molecules are similar as are their stereo-chemical configuration, there are certain notable differences. Stilbestrol is characterized by its highly unsaturated nature, and by the aliphatic nature of its side chain as contrasted with the cyclic structures in estradiol (B and C in fig 2).

The physiological response elicited by the synthetic estrogens in the therapeutic range has been shown to be identical with that of the natural hormones.

Most investigators believe on the basis of experimentation to date that the availability of estrogen to the animal organism, its metabolism, and its excretion are functions in which the liver plays a major rôle. When the natural estrogens are administered by mouth, the greater portion is metabolized by the liver during the process of absorption (3). With stilbestrol and other synthetic estrogens the degree of breakdown, while proportional to the rate of absorption and elimination, is considerably reduced. This difference in metabolism and absorption probably accounts for the greater oral potency of stilbestrol and also for the incidence of gastro intestinal upset that occurs with stilbestrol therapy.

For clinical use the most desirable estrogen would combine the following characteristics. It should be a), non toxic, b), of a high order of estrogenic activity regardless of the mode of administration, c), it should

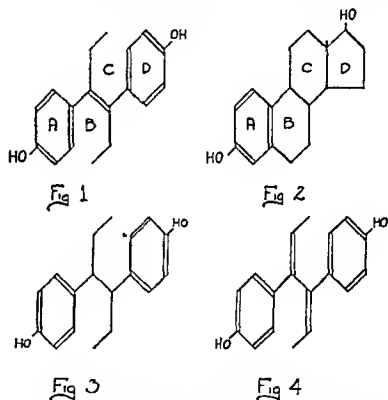


Fig 1 Diethylstilbestrol. Fig 2 Estradiol. Fig 3 Hexestrol.  
Fig 4 3,4-Bis(p-hydroxyphenyl)hexatriene

have a prolonged effect to obviate the necessity of frequent injections and d), should be inexpensive and readily available. The natural estrogens or their derivatives fulfill these requirements except for the disadvantage of being comparatively expensive and much less active by oral administration. Stilbestrol on the other hand although inexpensive and readily available has been found to give rise to undesirable side effects when used in dosage levels capable of producing a fully cornified vaginal smear. Also, stilbestrol, possibly because of its high solubility and ready availability for all organs produces an immediate rather than a prolonged estrogenic effect. Also, the oral effectiveness is well below that of the parenteral effectiveness.

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<sup>1</sup> The author is indebted to Dr. Franz C. Schmeltzer of the Wallace and Tiernan Products Company, Belleville, New Jersey, for the clinical supply of this material and for furnishing data on the chemical aspects of the compound.

The possibility of suitably modifying the stilbestrol molecule in order to produce the desired physiological effects was therefore investigated. Although a wide variety of modifications of the basic molecular structure of stilbestrol have been reported, as yet no definite correlation between chemical structure and estrogenic activity can be made. Comparatively few changes in the molecule are possible without a decrease in potency. The central double bond may be saturated as in hexesterol (fig. 3), or a second

TABLE 1. ESTROGENIC ACTIVITY OF DI-ALKYL ETHERS OF STILBESTROL

| $\approx$<br>1 R.U.       |              |              |              |
|---------------------------|--------------|--------------|--------------|
| Methyl                    | 25 $\mu$ g.  | Hexyl        | 30 mg.       |
| Ethyl                     | 50 $\mu$ g.  | Heptyl       | 750 $\mu$ g. |
| Propyl                    | 250 $\mu$ g. | Octyl        | > 50 mg.     |
| Butyl                     | 250 $\mu$ g. | Nonyl        | 5 mg.        |
| Amyl                      | 600 $\mu$ g. | Decyl        | 50 mg.       |
| Hexesterol dimethyl ether |              | 50 $\mu$ g.  |              |
| Hexesterol diamyl ether   |              | 600 $\mu$ g. |              |

These assay values along with the melting point of the compound have been previously published by Dr. E. E. Reid and Dr. E. Wilson (5).

double bond may be introduced as in 3,4 bis p-hydroxy phenyl hexadiene 3,4 (fig. 4) without decreasing the potency.

Variation in the length of the side chains has been reported by Dodds and his collaborators (1) to result in decreased activity. Thus stilbestrol is two or three times as active as the corresponding compound in which 1 of the 2 ethyl groups has been replaced by a methyl group; four to six times as active as the compound in which both ethyl groups have been replaced by methyl groups; and 20 to 30 thousand times as active as the compound where both ethyl groups are replaced by hydrogen. Lengthening of the side chain, as in the compound where both ethyl groups have been replaced by n-propyl groups decreases the potency several hundred times.

It is noteworthy that these compounds in common with other hormones differ in the potency of their stereo and geometric isomers. Stilbestrol, which is supposed to have the *trans* configuration of the substituents about the central bond, seems to be considerably more active than the purest *cis* isomer thus far prepared.

Dodds and co-workers prepared various esters of stilbestrol with aliphatic acids. They reported that the esters although somewhat less active than the parent compound produced prolonged estrus in rats. Clinical evidence of activity, particularly of the dipropionate ester, indicates that some of the untoward side effects of stilbestrol therapy have been removed, and a prolongation of the period of vaginal cornification achieved.

The observations that methyl ethers of various biologically active materials such as vitamin K, estradiol and estrone may be utilized in the animal organism presumably after demethylation led us to investigate the activity of di-alkyl ethers of stilbestrol. Since we began our investigation Sondern, Sealey and Kartsonis reported the activity of stilbestrol, the dimethyl, the di-ethyl and the di-propyl ethers to be in the ratio of 1:5:10:33. In table 1 we record similar but more extensive data. Although one obtains the desired prolongation of effect with the di-alkyl ethers of stilbestrol, the materials are somewhat too inactive for clinical utilization, and the duration of estrogenic effects is difficult to control.

In an effort to enhance the activity of the di-ethers while still maintaining the prolonged estrogenic effect we have assayed various mono ethers of stilbestrol and hexesterol.<sup>2</sup>

Table 2 shows the assay values obtained. As in the di-ether series, the estrogen value of these derivatives is reduced with increasing chain length.

The mono ethers of hexesterol are significantly less active than those of stilbestrol. This fact presumably arises from the greater ease of demethylation of the stilbestrol mono ethers as compared to the hexesterol mono ether.

The monomethyl ether of stilbestrol was carefully examined. It was found to be almost as active by oral administration as by intramuscular injection, the ratio being 1.25 to 1.0. By mouth it is only slightly

TABLE 2. ESTROGENIC ACTIVITY OF MONO-ALKYL ETHERS OF STILBESTROL

| $\approx$<br>1 R.U.         |               |              |              |
|-----------------------------|---------------|--------------|--------------|
| Methyl                      | 2-2½ $\mu$ g. | Octyl        | 50 $\mu$ g.  |
| Ethyl                       | 5 $\mu$ g.    | Nonyl        | 84 $\mu$ g.  |
| Propyl                      | 17.5 $\mu$ g. | Decyl        | 200 $\mu$ g. |
| Butyl                       | 20 $\mu$ g.   | Undecyl      | 100 $\mu$ g. |
| Amyl                        | 48 $\mu$ g.   |              |              |
| Hexyl                       | 45 $\mu$ g.   |              |              |
| Heptyl                      | 50 $\mu$ g.   |              |              |
| Hexesterol monomethyl ether |               | 8 $\mu$ g.   |              |
| Hexesterol monobutyl ether  |               | 50 $\mu$ g.  |              |
| Hexesterol monoamyl ether   |               | 150 $\mu$ g. |              |

These assay values along with the melting point of the compound have been previously published by Dr. E. E. Reid and Dr. E. Wilson (5).

less active than stilbestrol and is several times as active as estrone. In fact, its activity by mouth approaches that of estrone by injection. Injections of amounts well above the threshold estrogenic dose result in prolonged estrogenic effects, the prolongation being in proportion to the dose (table 3B).

<sup>2</sup> Some of these derivatives were kindly furnished by Dr. E. E. Reid and Dr. E. Wilson. Others were obtained from the Research Department of the Wallace & Tiernan Products Company.

## CLINICAL EVALUATION OF STILBESTROL MONOMETHYL ETHER

The use of estrogens in the menopausal syndrome is a substitutive form of therapy designed to replace absent or diminishing ovarian function. The results of treatment in such cases have become the accepted standard of clinical effectiveness of the various natural and synthetic estrogens. A series of 19 cases with the menopausal syndrome was selected for treatment with the monomethyl ether of stilbestrol. Ten of these were surgical castrates and 9 were patients with senile ovarian changes.

In general, the plan of treatment was to give the hormone by intramuscular injection in sesame oil once weekly for several doses (usually 10 to 15 mg for a

injections without a return of symptoms. In several patients in which the symptoms appeared within a few weeks following surgical castration, oral therapy only was administered. No untoward reactions were observed with oral therapy. Two patients were

TABLE 3B COMPARISON OF POTENCY OF ESTROGENS AND OF THE DURATION OF THEIR EFFECT WHEN INJECTED<sup>1</sup>

| Estrone                         |   |
|---------------------------------|---|
| Threshold, 1 to 2 µg            | Prolongation 10X, 1 to 2 days<br>25X, 1 to 2 days   |
| Stilbestrol                     |   |
| Threshold, 0.3 µg               | Prolongation 10X, 2 days<br>25X, 2 to 4 days        |
| Monomethyl-Ether of Stilbestrol |   |
| Threshold, 2 µg                 | Prolongation 10X, 5 to 9 days<br>25X, 10 to 45 days |

<sup>1</sup> Prolonged effects have not been obtained by oral administration.

TABLE 3A. COMPARATIVE EFFECTIVENESS OF ESTROGENS ORALLY AND PARENTERALLY

|                               |              | µg ≅ I R U |
|-------------------------------|--------------|------------|
| Estrone                       | By injection | 1-2        |
|                               | By mouth     | 7.5-15     |
| Stilbestrol                   | By injection | 0.2-0.3    |
|                               | By mouth     | 0.6-1.0    |
| Stilbestrol mono methyl ether | By injection | 2.0        |
|                               | By mouth     | 2.5        |

period of 1 month) and then to give a maintenance dose by mouth (usually 1 mg each night). This regime, however, was varied considerably. In some cases, the patients were maintained on injections for a period of months in order to determine the interval of time that might be permitted to elapse between

nauseated and vomited following parenteral injections of 15 mg, but therapy was resumed without encountering any difficulty at a lower dosage level. In another patient, nausea appeared after the injection of 25 mg.

In general 10 to 15 mg of monomethyl ether of stilbestrol are sufficient to inhibit the menopausal syndrome (hot flushes, giddiness, throbbing in the head and headache) for a period of 1 week. With doses of 25 mg by injection, treatment may be spaced as far apart as 3 or 4 weeks. With doses as low as 10 mg no reactions occur, but occasional nausea is encountered with 15 or 25 mg dosages. Once the menopausal reactions have been controlled by injections, the patients can usually be maintained on 1 mg daily by mouth for an indefinite period. In an occasional

TABLE 4. CASTRATES WITH MENOPAUSAL SYNDROME TREATED WITH MONOMETHYL ETHER OF STILBESTROL

| Case, and Age | Indication for Castration               | Injection |             | Subsequent Oral Medication mg/day | Results   | Reactions               | Number of month Treated |
|---------------|---|-----------|-------------|-----------------------------------|-----------|-------------------------|-------------------------|
|               |   | Dose mg   | Interval wk |                                   |           |                         |                         |
| EP 42         | Cystic ovaries, endometrial hyperplasia |           |             | 2                                 | Good      | None                    | 3                       |
| KB 34         | Pelvic inflammatory disease             | 5         | 1           | 1                                 | Good      | Nausea twice            | 9                       |
| RC 41         | Myomatous uterus                        |           |             | 1                                 | Excellent | None                    | 9                       |
| MS 32         | Lumbar neuroblastoma <sup>1</sup>       | 25        | 2           | 1                                 | Excellent | None                    | 2                       |
| GH 51         | Endometrial hyperplasia                 | 10        | 2           | 1                                 | Excellent | Nausea, once with 25 mg | 10                      |
| MW 40         | Uterine and intraligamentous myoma      | 25        | 2           |                                   |           | None                    |                         |
| FN 45         | Myomatous uterus                        | 10        | 2           | 1                                 | Good      | Nausea with 15 mg       | 3                       |
| MM 49         | Myomatous uterus                        |           |             |                                   |           | None                    |                         |
| NW 40         | Pelvic inflammatory disease             | 10        | 2           | 1                                 | Excellent | None                    | 3                       |
| HM 23         | Pelvic inflammatory disease             |           |             | 1, 3X, 1                          | Good      | Some nausea             | 3                       |

<sup>1</sup> Castration result of repeated irradiation.



case as much as 2 to 5 mg. daily may be required. In mild cases, particularly for symptoms appearing within 2 to 3 weeks after castration, oral medication alone is frequently adequate.

In table 4 and in the case histories the results of therapy are presented in more detail.

*Mrs. G. H.* The patient, aged 51, has been married for 29 years. She has two children and had two abortions. On June 5, 1940, the uterus, tubes and ovaries were removed because of menorrhagia associated with subserous and intramural fibroids. In November 1940, she complained of hot flushes which came as frequently as every three or four hours. These were accompanied by dizziness and fullness in the head. Ten mg. of monomethyl ether of stilbestrol were injected intramuscularly once weekly. This dose was well tolerated, but there was a tendency for the flushes to return at the end of 5 days. The intramuscular dose was then increased to 15 mg. once weekly with complete control of flushes. This treatment was continued for 2 months. The dose was then increased to 25 mg. which controlled the flushes from 10 to 12 days. There was some nausea with the first dose but not with subsequent doses of 25 mg. At the end of 4 months, the patient was given tablets of monomethyl stilbestrol ether 1 mg. each. These were taken one every other night, but did not completely control the flushes. Three weeks later the dose was changed to 1 mg. every night. For the past 5 months, the patient has been doing well on this dosage.

*Mrs. M. W.* The patient, a married woman, aged 40, had attacks of abdominal pain for 4 years—the pain radiating across the abdomen and sometimes to the back. Most of the tenderness appeared to be low and in the midline. Palpation of the abdomen revealed a mass in the left adnexa. At operation, Aug. 30, 1938, a large intramural myoma and bilateral chocolate cysts of the ovaries were found. The appendix, uterus, tubes and ovaries were removed. The patient did well for one year after the operation; after which there was a return of abdominal distress. Another operation was performed for an intra-ligamentary parovarian cyst on Nov. 27, 1939. Following this, the patient improved and gained in weight. In 1940 she had gained 10 pounds and was free of abdominal distress. In December 1940, however, she was having hot flushes every 2 hours and was feeling nervous and tense. She did not have strength to complete a day's work. She was given 1 mg. of monomethyl ether of stilbestrol daily. Within a period of 2 weeks the patient had regained her normal energy and had lost her nervous, tense feeling. She has since been taking 1 mg. daily and has been free from symptoms in the past 6 months.

*Mrs. K. B.* The patient is a married woman aged 34 with two children, who had a previous hysterectomy 5 years ago. On Sept. 3, 1940 an exploratory laparotomy was done for adhesions, and both tubes and ovaries were removed. Since that time she has been having continual abdominal distress with nausea and frequent vomiting. She has had attacks of diarrhea and severe headaches and has lost 20 pounds in weight. Before the patient left the hospital in September 1940, she was having flushes and was

put on stilbestrol by mouth, 1 mg. every other day. However, within 2 weeks she returned complaining of constant nausea every morning with the spitting up of frothy material and repeated vomiting. Stilbestrol was discontinued and the headaches and flushes soon returned. On Oct. 30, 1940 she was given 15 mg. of monomethyl ether of stilbestrol intramuscularly. The night of the injection she vomited and was nauseated for the next 24 hours. The patient was not treated for 2 weeks, and was then given injections of 5 mg. once weekly which were well tolerated but which did not control the headaches. She was then given 1 mg. tablets to be taken by mouth one each day. These controlled the headaches and flushes. There was a tendency for fullness and loss of appetite after a period of 3 months, and the patient was put on parenteral administration and the tablets were decreased to one every other day. Early in August, 1941 there was a return of the flushes and headaches. The patient was given 15 mg. by injection in three equal doses of 5 mg. at 4-hour intervals to see if her tolerance had increased. Again there was nausea and vomiting, and the patient was returned to the use of 1 mg. tablets every day. The results have been satisfactory and there has been no nausea or headache.

*Mrs. F. N.* The patient, a married woman aged 45, had backache and abdominal pain. A tumor was palpated low in the pelvis. At operation in August 1939, both the uterus and ovaries were removed, but when the posterior peritoneum was incised the pelvic mass proved to be the left kidney. The appendix was removed and nothing further was done. The patient's abdominal complaints were relieved, but in February 1940 nervousness, fatigue and flushes became severe. The flushes occurred as frequently as every 4 hours. She was put on stilbestrol tablets, 1 mg. every other night. At the end of 5 days, there was a feeling of fullness, loss of appetite, and flatulence. She was given injections of estradiol benzoate, 1.6 mg. every week for the remainder of the year. In February 1941, the treatment was changed because the patient complained of a feeling of fatigue and depression during the first 2 days following the injection. An injection of 2 mg. of stilbestrol intramuscularly was tried, but the patient vomited 5 times during the night. She was then put on 1 mg. of estrone parenterally twice weekly. Treatment was continued for several months with control of symptoms. Ten milligrams of estrone were then implanted in the back in the form of three pellets. Again, the patient had a feeling of depression and fatigue for several days followed by 2 or 3 weeks in which the symptoms were controlled. In June 1941, the patient was put on tablets of monomethyl ether of stilbestrol, one every other night. These were well tolerated, but did not completely control the feeling of fatigue and hot flushes.

*Mrs. R. M.* This patient, aged 40, had a spontaneous menopause. The patient had flushes every one-half to 4 hours. Stilbestrol monomethyl ether tablets, 1 mg. daily were given for 3 weeks with complete relief of symptoms. After 6 months without treatment, there was recurrence in a mild form and 1 mg. every 2 days for 2 weeks was administered. Thereafter, the medication was given only at the appearance of the flushes, but not more than 1 mg.

daily The symptoms are controlled on 1 or 2 mg each month at the present time She has no untoward symptoms

Miss E W This patient, aged 43, had a spontaneous menopause The patient had flushes every 2 to 4 hours which required 2 mg of estrone 3 times weekly for complete relief She could not take stilbestrol because of nausea The patient was put on stilbestrol monomethyl ether, 1 mg daily, with complete relief for 3 months of treatment She has had no untoward symptoms and is perfectly comfortable She has not needed any medication for the past 2 months

In addition to the 19 cases of menopausal syndrome just discussed there were thirty cases with a variety

of cases with dysmenorrhea were given 1 mg. of stilbestrol monomethyl ether daily for 10 days preceding the menstrual period The majority reported improvement The patients who were depressed in the premenstruum received 1 mg either daily or every other day. The majority of these cases noted increased libido and enlargement of their breasts All tolerated the drug well. None of the patients in this group developed amenorrhea

Four cases of painful breasts, 2 complicated by adenosis, were treated with 1 mg-tablets daily over a period of 2 months, treatment thereafter being discontinued All of these patients were improved and noticed an increase in the size of the breasts

TABLE 5 MENOPAUSAL SYNDROME WITH SENILE OVARIAN CHANGES TREATED WITH MONOMETHYL ETHER OF STILBESTROL

| Case and Age | Injection   |               | Subsequent Oral Medication   | Results  | Reactions         | Number of Month Treated |
|--------------|---|---------------|--|--|-------------------|-------------------------|
|              | Dose mg   | Interval days |  |  |                   |                         |
| Da 39        | 25  | 28            | 1 mg every other day   | Excellent  | None              | 9                       |
| Be 40        | 10  | 7             |  | Excellent  | None              | 3                       |
| Ei 49        | 15  | 10            |  | Good   | None              | 2                       |
| Fr 43        | 15  | 1             | 1 mg daily   | Excellent  | None              | 6                       |
| Ly 51        | 10  | 7             |  | Good   | None              | 2                       |
| R M 49       |   |               | 1 mg daily for 6 mo<br>Thereafter, 1 mg every 2 days or for flushes only | Patient finally controlled by about 2 mg monthly | None              | 6                       |
| E W 43       | Previously treated estrone then stilbestrol tried, discontinued because of nausea |               | 1 mg daily   | Excellent  | None              | 3                       |
| E M 47       | 5 3X/wk Menstrual bleeding when discontinued 5 mg 3X weekly then resumed          |               |  | Excellent  | None              | 5                       |
| E A 46       | 5 3X/wk   |               | 1 mg daily   | Excellent  | None <sup>1</sup> | 3                       |

<sup>1</sup> The patient vomited twice, but was a diabetic and when disease controlled with insulin the nausea disappeared

of other conditions which were treated with stilbestrol monomethyl ether In these cases the drug was administered orally in 1 mg doses daily and occasionally in larger amounts

There were 6 cases of hypogonadism, the majority with the girdle type of obesity and loss of energy With one exception, these patients had scanty menstruation and were between the ages of 16 and 24 The treatment consisted of 1 mg of stilbestrol monomethyl ether and 3 grains of thyroid daily The drug was well tolerated and clinically effective as judged by the increased energy and decreased weight These patients showed a tendency to amenorrhea unless the estrogenic treatment was discontinued at intervals or progesterone injections (5 mg once weekly) were added

A group of 14 cases with menstrual disorders, including young girls with dysmenorrhea and women in their late thirties or early forties, with lassitude and depression in the premenstruum, was treated The

Stilbestrol monomethyl ether was used in doses of 2 5 mg daily by mouth along with diacalcium phosphate wafers, vitamin D and a diet rich in calcium and phosphorus to stimulate ossification in 6 cases with bone lesions The drug was well tolerated and ossification was usually stimulated In one case of osteogenic sarcoma, the patient had metastasis to the lungs with severe cough and was bedridden Remarkable improvement occurred and the patient has been symptomatically relieved for 9 months The affected leg had been previously amputated In a case of pituitary gigantism treated with 5 mg of the drug daily by mouth, further growth was arrested This patient developed gynecomastia and complained of loss of appetite One of the patients with giant cell tumor, treated by curettage, could not take the drug in 2 5 mg doses because of vomiting

#### Toxicity of Stilbestrol Monomethyl Ether

In our experience the toxicity of estrogenic com-

pounds must be based largely upon clinical data, since to date no toxic effects have been found in animal experimentation which would permit a quantitative comparison of the toxicity of the various estrogens. Morrell (2), in tabulation of 64 published papers on the clinical use of stilbestrol in 4,507 cases, lists only three authors (reporting on 304 cases) who found no untoward side reactions with the use of this

TABLE 6. EFFECTIVENESS OF VARIOUS ESTROGENS IN THE PRODUCTION OF MAMMARY CANCER IN SUSCEPTIBLE RATS

| Estrogen   | Potency <sup>1</sup> | Dosage  | Av. Time for Cancer | Rats with Cancer | Total dose | Dosage factor <sup>2</sup> |
|--|----------------------|---------|---------------------|------------------|------------|----------------------------|
|  | µg.                  | µg./day | days                | %                | mg.        |                            |
| <i>Injections, estrogen without prolonged action</i> |                      |         |                     |                  |            |                            |
| Estrone  | 1.0                  | 200     | 203                 | 80               | 34.8       | 34.8                       |
| Estrone  | 1.0                  | 100     | 383                 | 100              | 32.8       | 32.8                       |
| Estrone  | 1.0                  | 50      | 548                 | 75               | 32.5       | 32.5                       |
| Stilbestrol  | 0.3                  | 200     | 104                 | 100              | 17.8       | 59.3                       |
| Stilbestrol  | 0.3                  | 100     | 212                 | 100              | 18.2       | 60.8                       |
| Estradiol  | 0.3                  | 100     | 290                 | 50               | 25.0       | 83.3                       |
| <i>Injections, estrogen with prolonged action</i>    |                      |         |                     |                  |            |                            |
| Stilbestrol monomethyl ether                         | 2.0                  | 50      | 212                 | 50               | 9.5        | 4.8                        |
| Stilbestrol dimethyl ether                           | 25.0                 | 500     | 233                 | 17               | 116.5      | 4.6                        |
| Estradiol benzoate                                   | 0.6                  | 200     | 120                 | 67               | 23.6       | 39.2                       |
| Estradiol benzoate                                   | 0.6                  | 100     | 120                 | 63               | 11.8       | 19.6                       |
| Estradiol enzoate                                    | 0.6                  | 5       | 120                 | 100              | 0.6        | 1.0                        |
| Estradiol ipropionate                                | 0.5                  | 100     | 255                 | 75               | 21.8       | 43.6                       |
| Estradiol ipropionate                                | 0.5                  | 5       | 120                 | 40               | 0.6        | 1.2                        |
| <i>Pellets</i>                                       |                      |         |                     |                  |            |                            |
| Estrone  | 1.0                  | 5       | 273                 | 50               | 9.6        | 9.6                        |
| Stilbestrol  | 0.3                  | 5       | 105                 | 20               | 10.1       | 33.6                       |
| Estradiol  | 0.3                  | 3       | 310                 | 67               | 8.0        | 26.6                       |
| Estradiol ipropionate                                | 0.5                  | 4       | 280                 | 67               | 10.0       | 20.0                       |

<sup>1</sup> Potency indicates the number of micrograms of crystalline hormone necessary to produce full estrus in 50% of the animals (as measured by the vaginal smear) in the author's colony of white rats.

<sup>2</sup> Dosage factor is obtained by dividing the total number of mg. necessary to produce cancer by the estrogenic potency of the hormone.

drug. These reactions included, in the order of their frequency, nausea, vomiting, loss of appetite, abdominal distress, headache, diarrhea, drowsiness, vertigo, palpitation, and skin eruptions. Only during pregnancy and the puerperium are toxic manifestations uniformly absent. Liver function studies, blood morphology, blood chemistry, and studies of the urine revealed no significant findings in the cases reviewed by Morrell. The percentage of untoward side reactions increases with the size of the dose.

When administering stilbestrol compounds for a specific effect such as the control of menopausal symptoms, other physiological effects such as increase in the size of the breasts and pigmentation of the nipples, accentuation of libido and delayed or increased uterine bleeding are observed. The effects on mammary development and on uterine bleeding apparently are slightly more pronounced with stilbestrol compounds than with other estrogens.

The five instances of untoward reactions observed by the author in 49 patients treated with the monomethyl ether of stilbestrol are in general similar to those found when stilbestrol is administered, but occur in a smaller percentage of cases and are practically absent in women when the oral method of administration is used. With oral therapy loss of appetite was observed in one patient receiving 5 mg. daily; in another patient, there was vomiting with 2.5 mg. doses. Both of these were boys aged 16 and 17 in whom the drug was used to promote ossification. Since the oral potency of stilbestrol monomethyl ether is approximately the same as that of stilbestrol, it is our impression that the former drug is definitely better tolerated when given by mouth.

Thus, patients who were unable to take stilbestrol by mouth, were able to take corresponding doses of the monomethyl ether. When intramuscular injections are used, the gastro-intestinal symptoms depend upon the size of the dose. In general, injections of from 10 to 15 mg. in oil which will control menopausal symptoms for 7 to 10 days are well tolerated. With high doses of from 15 to 25 mg. untoward reactions will be observed in some cases, but these are usually confined to the initial dose.

#### Cancerigenic Effects

The comparative cancerigenic effect of a variety of estrogenic compounds on the mammary gland of the rat is the subject of a separate communication. For the sake of brevity, only the following data are recapitulated here (table 6).

The rapidity with which the mammary cancer appears, the percentage of affected animals, the type of changes preceding the cancer, and the pathologic form of the cancer are affected by increased dosage, physiologic potency, duration of the estrogenic action and the period of administration of the estrogenic compound, but not by its chemical structure. The pre-existing state of the mammary gland, the absence or presence of the gonads or the pituitary, and the age of the animal have also been found to be of importance.

The most commonly overlooked factor in studies of this kind is the strain or species susceptibility of the experimental animal. While the rats on which these experiments were performed belong to a strain in which mammary cancer does not occur spontane-

ously, nevertheless, their susceptibility to estrogenic mammary cancer is definite. In other strains of rats such as those described by Zondek, there was a marked resistance to estrogenic mammary cancer. A similar resistance has been found by us in the experiments performed on the white rabbit and on the rhesus monkey.

When estrogens are given in sufficient doses over a sufficient period to produce mammary cancer, there are also profound changes in the endocrine organs and in accessory sex structures. Marked reduction in weight and various forms of atrophy accompanied by tumor formation occur in the gonads, the anterior pituitary, the thymus and in the adrenals.

Stilbestrol and its ethers are similar in their effects to the natural estrogens when given above physiological levels for prolonged periods. The number of mammary cancers produced and the time of their appearance when stilbestrol monomethyl ether is administered is in proportion to its estrogenic potency and the delayed rate of absorption when considered in relation to the natural estrogens.

Approximately 10 mg of stilbestrol monomethyl ether are required to produce cancer in 50 per cent of the rats in 212 days. The same amount is required if stilbestrol or estrone is used in the form of pellets to obtain a prolonged action. With the estrone pellets, the cancer appeared within 273 days, and with stil-

bestrol in 105 days. The estradiol compounds which have a prolonged action such as the benzoate and the dipropionate require far less of the hormone for cancer production. A total dose of 0.6 mg of estradiol benzoate or estradiol dipropionate will produce cancer in 120 days. These facts are brought out in table 6.

#### SUMMARY

A series of dialkyl ethers of stilbestrol have been assayed on the rat.

A series of monoalkyl ethers of stilbestrol and hexesterol have also been assayed.

Stilbestrol monomethyl ether has been found to be highly effective and comparatively nontoxic orally and by injection when used for treatment in the menopausal syndrome. The results of the clinical use of this drug in 49 cases are given.

The cancerigenic activity of stilbestrol monomethyl ether has been investigated and compared to that of other natural and synthetic estrogens.

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# Clinical Experiences with the Sublingual Administration of Alpha Estradiol

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## [[Vaginal Cornification]]

A NUMBER OF INVESTIGATORS have reported that when estrogens are administered orally a considerable proportion, as much as 90 per cent, is inactivated in the liver. Thus, in order to achieve the same estrogenic effect, ten times more material must be given by mouth than is necessary to achieve the same result by hypodermic injection. This same principle applies to other steroid hormones, except that in some cases the hormone is completely inactivated if given by mouth.

The original work by Anderson, Haymaker and Henderson (1) showed that when the steroid hormone, desoxycorticosterone acetate, was dissolved in a propylene glycol-alcohol solution it could be successfully administered sublingually in the treatment of Addison's disease. A number of investigators have applied this same principle to estrogens, androgens, and other hormones. Salmon and Geist (2) have shown that sublingual administration of alpha estradiol produces a typical cornified vaginal smear. The advantages of a highly active oral estrogen are obvious.

Clinical evaluation of various estrogenic materials must take into consideration the effects of large doses every 5 to 7 days, smaller doses 2 or 3 times weekly and still smaller doses daily.

Shorr (3) has reported: "The wider the interval between doses the less efficient is any total amount of hormone, over any given period, in maintaining the level of estrogenic replacement therapy; and for this reason every assay designed to compare the relative effectiveness of estrogens by different routes should keep this principle in mind. The most accurate comparative assays are carried out by daily administrations."

Following this line of reasoning, it would appear that if the daily doses were divided and given 3 or more times daily, the results should be better than one single large daily dose.

Vaginal smears, which show the various degrees of cornification of the vaginal epithelium, are considered the most accurate clinical tests for determining the

estrogenic levels. In this investigation, vaginal smears were the only tests used.

*Vaginal smear technique:* The vaginal material is collected from the lateral walls of the vagina with a curved spatula, spread thinly on a clean glass slide and dried with compressed air. The slide is then stained for 20 seconds with a 2% aqueous solution of basic fuchsin. Excess stain is removed with tap water and the slide is dried with compressed air. It is then ready to evaluate.

In April, 1941, the first series of 98 menopause types of patients was completed. In this series an effort was made to determine the comparative ratio of absorption of  $\alpha$ -estradiol in a solution of propylene glycol-alcohol administered sublingually to intramuscular injections. This material was the crystalline  $\alpha$ -estradiol dissolved in the glycol-alcohol solution in a concentration of 0.5 mg. or 6,000 Allen-Doisy R.U. per cc.

There is no question but that the technique of administration is of great importance if the best results are to be obtained. There is an optimum amount of solution that ought to be administered at one time, since, if a large volume of the propylene glycol-alcohol solution is administered at one time it mixes with salivary fluids and is likely to be swallowed. Experience shows that 1/10 cc. is suitable for one dose. If the solution is carefully applied one drop at a time, allowing a lapse of a few seconds between each drop, to the sublingual surface directly onto the visible sublingual veins, the absorption is good. This can easily be done by having the patient touch the roof of her mouth with the tip of the tongue and slightly tilt her head back, applying the first drop near the tip of the tongue at the point where the sublingual veins are first visible, and allowing it to trickle down. The single dose of 1/10 cc. (about 4 drops) should be applied in this manner, drop by drop, alternating the drops, on either side of the frenum. With a little practice in front of a mirror the patient will soon become adept and the solution can be administered without difficulty. A small pocket mirror will suffice when the patient is not at home.

If there is a tendency for salivary fluids to accumulate after administration of the solution, it is better for the patient to swallow the accumulated fluid a bit at a time rather than to swallow all of the material at one time. The surface tension of this solution is very low, 32 dynes per centimeter; thus, if only a small portion is swallowed it is believed that absorption will take place from the upper portion of the esophagus so that no material will reach the stomach.

This material was given to some patients who had been receiving hypodermic injections every 5 to 7 days. It required 0.20 mg daily sublingually (1/10 cc 4 times daily) or 2.0 mg in 10 days to obtain the results afforded by two injections of 1.666 mg. of estradiol benzoate at 5 day intervals. There was confirmation of Shorr's findings in the fact that those patients who had been receiving daily injections of 0.166 of estradiol benzoate to obtain the desired estrogenic level, obtained equal results with daily doses of 0.20 mg sublingually. It would seem, therefore, that the most rational comparison is with daily doses of both preparations (or routes of administration).

In a recent series of 41 patients an effort was made to determine the variation of the vaginal cornification over a period of 14 days. This was done because some patients seemed to maintain comfort and a high estrogenic level (as determined by vaginal smears) and others had a mild return of their former symptoms with these dosages. The findings are shown in the table.

RESULTS IN TERMS OF VAGINAL CORNIFICATION, OF 4 Doses DAILY OF 1/10 CC (OR 0.05 MG., 600 R U) EACH OF  $\alpha$  ESTRADIOL IN PROPYLENE GLYCOL-ALCOHOL SOLUTION ADMINISTERED AS DROPS ON UNDER SURFACE OF TONGUE

| Number of Cases  | Vag Smear Before Treatment | Vag Smear After 48 hr | Vag Smear After 96 hr | Vag Smear After 14 days |
|--|----------------------------|-----------------------|-----------------------|-------------------------|
| <i>Castrates, no recent therapy</i>                                      |                            |                       |                       |                         |
| 1  | +                          | +                     | ++                    | +++                     |
| 2  | ++                         | ++                    | +++                   | ++++                    |
| <i>Castrates, who had received intramuscular estrogens *</i>             |                            |                       |                       |                         |
| 1  | +++                        | +++                   | +++                   | ++                      |
| 3  | ++++                       | ++++                  | ++++                  | +++                     |
| 3  | +++++                      | +++++                 | +++++                 | +++++                   |
| <i>Menopause types, who had received intramuscular estrogens</i>         |                            |                       |                       |                         |
| 12   | ++++                       | ++++                  | ++++                  | +++                     |
| 3  | +++++                      | +++++                 | +++++                 | +++                     |
| 8  | ++++                       | ++++                  | ++++                  | +++++                   |
| <i>Hysterectomized patients who had received intramuscular estrogens</i> |                            |                       |                       |                         |
| 5  | ++++                       | ++++                  | ++++                  | +++                     |
| 3  | ++++                       | ++++                  | ++++                  | +++++                   |

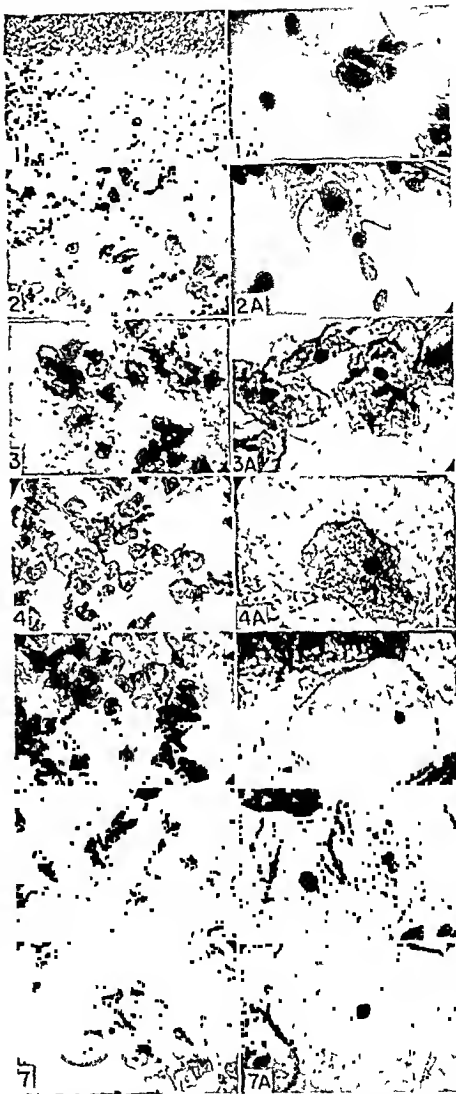


Fig 1-7 and 1A-7A PHOTOMICROGRAPHS OF VAGINAL SMEARS low and high magnification. Atrophic smear of artificial menopause in 1. Gradual change up to normal cornification in 5, 6 and 7.

Castrates, who had received no previous therapy, showed improved vaginal cornification at the end of 14 days. Four castrates, who had received recent intramuscular estrogens, showed a slight reduction of

vaginal cornification after 2 weeks of sublingual estradiol, and 3 maintained a high degree of cornification throughout the period of the test.

Fifteen menopause types showed a slight reduction of cornification, whereas 8 patients had smears giving evidence for an improved estrogenic level. Five hysterectomized patients had a slight reduction after 14 days therapy and 3 were definitely improved.

Twenty-four of 41 patients did not maintain quite the same estrogenic level, 3 maintained the original high level and 14 showed much improvement. Those patients who did not quite maintain the required level were given an intramuscular injection of 10,000 R.U. of estradiol benzoate followed by 1/10 cc. of the sublingual estradiol solution 5 times daily (instead of 4) with completely adequate results. Therefore, individualization of dosage is required and effective clinical results are obtainable with this method of administration.

These findings justify the belief that the  $\alpha$ -estradiol in propylene glycol-alcohol solutions used sublingually in this investigation produces the same effects on vaginal cornification as the estradiol benzoate administered parenterally.

It will be seen that over a period of 14 days almost comparable results were obtained by the sublingual administration of 2 mg. of  $\alpha$ -estradiol when compared with injections of 3.33 mg. during a like period. About one-half of the patients showed a slight regression on the lower sublingual dosage. Undoubtedly, if the same amount of material in milligrams had been given sublingually as given by injection, results would have been exactly comparable.

It may be concluded, therefore, that the sublingual administration of  $\alpha$ -estradiol in a propylene glycol-alcohol solution is equally as effective milligram for milligram as  $\alpha$ -estradiol benzoate given by hypodermic injection.

I am greatly indebted to Dr. Edward Henderson of the Medical Research Division, Schering Corporation, Bloomfield, New Jersey, for supplying material for these studies.

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# Sexual Infantilism of Hypothyroid Origin

## [Thyroid and Infantilism]

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FOR MY ADDRESS as President of The Association for The Study of Internal Secretions in 1928 (1) the title "The Uniglandular Origin of Pluriglandular Diseases" was chosen. In the address was the statement "The overwhelming majority of endocrinopathies which we are justified in diagnosing exhibit a predominantly uniglandular basis, which anyone properly trained in endocrine diagnosis should be able to recognize. This conception (for which no originality is claimed) is a fundamental and controlling basis for the proper interpretation of endocrine syndromes. An unanalyzed syndrome is a quicksand for therapy. A firm foundation for inductive therapy demands a sharply defined analysis of the symptoms and signs, with emphasis on the gland primarily responsible." A diagnosis of 'pluriglandular dystrophy' or 'multiglandular syndrome' is often merely camouflage for ignorance.

This thesis is abundantly confirmed by such well established endocrinopathies as gigantism, acromegaly, hypophyseal cachexia (Simmonds' disease), hypophyseal infantilism, exophthalmic goiter, myxedema, osteitis fibrosa cystica, tetany, Addison's disease, masculinization due to arrhenoblastoma or an adrenal cortical tumor, sexual precocity due to lesions of the ovary, the testicle, the adrenal cortex or the epiphysis cerebri, eunuchism and hypogonadism, all of which have their primary specific gland focus whose functional derangement causes secondary disturbance in one or more other ductless glands.

In logical sequence therefore "a diagnosis which fixes the responsibility for a clinical complex, ipso facto, like a compass, points the direction by which one should steer one's therapeutic course" (1). A pluriglandular mixture would be sadly futile in the treatment of an amenorrhea due to acromegaly, an arrhenoblastoma of the ovary, or an adrenal cortical tumor, or to anorexia nervosa.

Though the author shares the justified enthusiasm for the newer, remarkably potent synthetic sex hormones, the following case illustrates that these were neither necessary nor primarily indicated in a case of sexual infantilism recognized as due to hypothyroidism.

The patient, a 27 year old unmarried woman, was first seen in April 1939, and she was quite uninterested in the opposite sex. She was an only child. Nothing in her past or family history seemed to have any significance. She had always lived close to San Francisco bay.

Her complaints were shortness of stature (4 ft 10 3/4 in, father and mother were fairly tall), eczema for 10 years, tendency to gain weight easily, and inability to run normally ("legs won't work").

The menarche occurred at 16 years of age, somewhat late, the flow was scanty, and the intervals between periods averaged 5 to 6 weeks but occasionally were lengthened to 2 months. The term 'sexual infantilism' used in the title might be considered an exaggeration, but a glance at her photographs will disclose almost complete absence of secondary sex characteristics (fig 2, A and 3, A), there were 2 or 3 hairs on the labia, none on the pubes. There was no axillary hair. Breast development was barely perceptible, little if any mammary tissue being palpable, the nipples and areolae were like a child's. By rectal examination the uterus felt small and the adnexae could not be palpated. In harmony with her severe sexual retardation she had an appearance fully 10 to 15 years younger than her chronological age.

She claimed to have grown normally until 12 years of age when for no apparent reason growth ceased, although she had no accurate records to substantiate this. Her sexual immaturity permitted the prediction that the 'bone age' would be similarly retarded and such was the case, it was estimated at 14 years when she was 27 years old. The epiphyses of the long bones were incompletely fused with the shafts. All the bones were small and the roentgenograms showed evidence of deficient calcium but without disturbance of bony architecture. The sella turcica was considered to be within normal limits.

The patient admitted a preference for warm weather and a sensitiveness to cold temperatures, she perspired very little. Her temperature was subnormal, 97° F. Her skin and scalp hair were very dry. Two bald spots had developed 8 years before but had responded to scalp treatments which had to be continued regularly. Her arms and legs were entirely de-



void of hair. She had been constipated for many years, constantly requiring cathartics. She was not drowsy in the daytime but slept 9 to 10 hours nightly. She tired easily and had never felt able to work, but she had finished 3 years of college obtaining average grades. Although she was not obviously weak or clumsy, weak leg muscles and stiff knee joints prevented her from running; there was no ataxia. Since 12 years of age, food intake restriction was necessary to prevent obesity. The patient's pulse rate was definitely slow, 58 to 66; her blood pressure 98/70 mm. Hg. The thyroid gland was barely palpable and

ance 10 to 15 years younger than her age of 27 years. Should this case be classified and interpreted as a) hypophyseal infantilism, b) mild Simmonds' disease, c) avitaminosis, d) ateliosis, e) insuffiance pluriglandulaire, f) multiple ductless glandular sclerosis, or g) primary hypothyroidism without outright childhood myxedema?

The writer in lectures to medical students and post-graduates, has emphasized the practice of prescribing, wherever possible, one gland extract rather than several, if for no other reason than to be able to judge later on what medication did what. Frequently

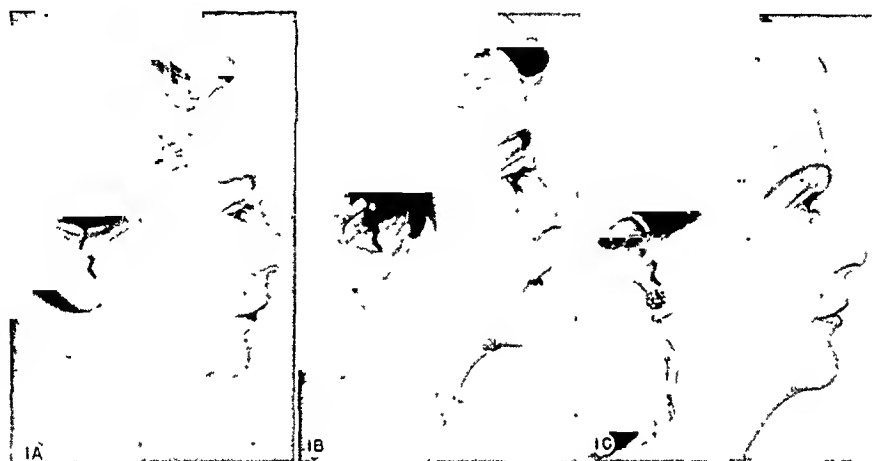


Fig. 1. PROGRESSIVE CHANGES IN APPEARANCE OF 27-YEAR-OLD PATIENT WITH HYPOTHYROIDISM RECEIVING THYROID THERAPY. A, 4/21/39, at outset of treatment; B, 9/25/39, 5 months after beginning thyroid therapy; C, 3/4/41, thyroid continuously and 1 mg. of stilbestrol daily beginning 4/8/40.

certainly was quite small. Careful scrutiny of the features suggested a little puffiness under the eyes which was suspicious of a mild myxedema. The photograph of the patient taken after several months of thyroid therapy, shows a change so startling as to make the original puffiness quite apparent; actually this was barely discernible at first (fig. 1A, B, and C). A B.M.R. of  $-27\%$  helped to reinforce the clinical impression. Furthermore a certain pallor was corroborated by a hemoglobin value of  $50\%$  and a red cell count of 2,960,000. This anemia strengthened the supposition of hypothyroidism. A glucose tolerance curve was rather flat: 73, 89, 123, 78, 79, 80 and 75 mg. per 100 cc. of blood.

In this case there were signs and symptoms pointing to thyroid, anterior pituitary, ovarian and possibly adrenal involvement in a multiglandular confusion. There was shortness of stature without actual dwarfism, markedly retarded ossification, fairly normal weight due to dietary restriction, sensitivity to cold, constipation, bradycardia, hypotension, anemia, low B.M.R., slight puffiness of the face, late onset of scanty and somewhat infrequent menstrual periods, absence of secondary sex characters, and an appear-

in complicated or perplexing cases it subsequently becomes necessary to add some other hormone to achieve additional effects if the original hormone failed to supplement completely for the endocrine deficiencies.

Believing that this patient's symptom complex was ascribable primarily to adolescent hypothyroidism, thyroid was prescribed, at first in doses of  $\frac{1}{2}$  grain daily of the desiccated substance. Three weeks later this was increased to 1 grain daily. One month after beginning therapy the B.M.R. had risen from  $-27.3\%$  to  $-21.7\%$ . By this time greater alertness and animation was noticeable and commented upon by the patient's mother.

Five weeks after commencing treatment unmistakable evidence of beginning breast development was apparent. The puffiness under the eyes had almost disappeared. The patient felt warmer and was much more active. The dose was increased further to  $1\frac{1}{2}$  grains daily. Two months after therapy was begun the B.M.R. had reached the normal level of  $-4.7\%$ .

Three months after instituting thyroid therapy, the dose of the desiccated substance was increased further to 2 grains daily. By this time, and on thyroid

substance alone, the hemoglobin had risen slightly from 50 to 53%, and the red cell count had increased significantly from 2,960,000 to 3,900,000. This specific stimulus to red cell production has been reported previously, notably in a case of masked myxedema with a blood picture simulating pernicious anemia (3).

By the time 4 months had elapsed from the start of treatment the mammary development was most impressive, with firm well formed breasts. The pubic (strictly labial hair growth) remained sparse. No axillary hair had appeared.

Remarkable evidence of the transformation which had occurred, not only in appearance but also in psyche, demeanor and physiological impulses was the admission by the patient, 9 months after beginning treatment, that she feared she might be pregnant—this in contrast to her total lack of interest in the opposite sex 9 months before. She volunteered strong libido and intense gratification. She had planned marrying 2 months later. An Ascheim Zondek test was negative.

The menstrual intervals, prior to thyroid therapy, had averaged between 5 and 6 weeks, and occasionally were lengthened to 2 months. The period dates since beginning treatment have occurred as follows: 4/10, 5/25, 7/7, 8/2, 8/29, 9/26, 10/22, 11/16, 12/12/39, 1/19/40. It was the delay in the January period following 'exposure' which occa-

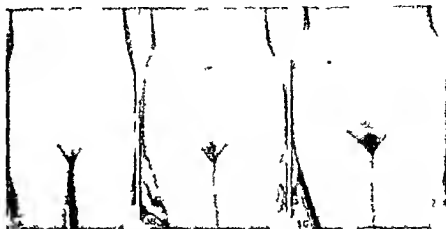


Fig 3 A 4/21/39 before thyroid therapy, B 2/6/40 9 months later, C 3/4/41, thyroid continuously 1 mg of stilbestrol daily since 4/8/40

sioned the alarm about pregnancy. It is to be noticed that the intervals had been shortened to 25 to 26 days, as a rule.

The patient was married in February 1940. Her altered appearance at this time may be observed in figures 1, 2 and 3. She now was an alert, vivacious, pretty, well developed woman. She had gained 16 pounds, but had grown at 27 years of age only 5/8 of an inch.

In April 1940, after 1 year of treatment consisting solely of thyroid substance, it was reasonable to assume that no further improvement could be anticipated. It was decided to add estrogenic stimulation in the form of stilbestrol, in the hope of inciting greater growth of pubic hair which was still rather scanty. No axillary hair had appeared. Furthermore, though the breasts were well developed, the nipples remained flat and slightly inverted (fig 2, A and B). The dose prescribed was 1 mg daily, orally.<sup>1</sup> In addition she continued to take 2 grains of thyroid substance daily.

Stilbestrol in the enteric tablets form caused no unpleasant side effects, but it is worthy of note that subsequently, on uncoated tablets, the patient became nauseated. This disappeared again when coated tablets were resumed (the dose being the same).

The stilbestrol medication rather promptly provoked protrusion of the nipples, with the usual dark pigmentation of the nipple areolae. More gradually, increased growth of pubic hair became apparent but even a year later the amount was by no means normal.

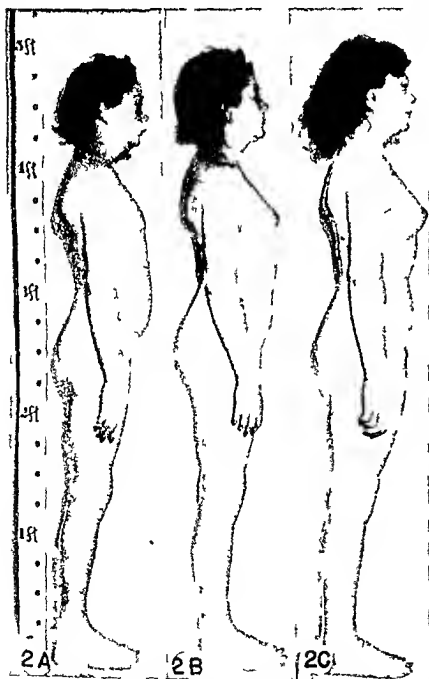


Fig 2 A 4/21/39 before thyroid therapy B 2/6/40 9 months later C 3/4/41 thyroid continuously and 1 mg of stilbestrol daily since 4/8/40

<sup>1</sup> The stilbestrol capsules used came from a generous supply furnished by Eli Lilly Co., Indianapolis, Indiana.

(fig. 3, A, B, C). The first axillary hair appeared 8 months after stilbesterol was started and only 3 or 4 short hairs in the right axillae are present after 14 months. Stilbestrol given daily had an unfavorable effect on the regularity of menstruation; the patient was employing contraceptive measures to prevent pregnancy. After several months its administration was confined to 2 weeks between periods; thereafter the periods resumed regularity.

Altogether the patient gained 20 lbs. and for some time has been slightly curtailing her appetite to prevent further gain. She is in excellent health, cheerful, animated and her sexual ardor is thoroughly normal. She continues to take 2 grains of desiccated thyroid daily, and the last B.M.R. (December 1940) was  $+4.6\%$ . She continues to take stilbestrol, 1 mg. daily for 2 weeks between periods in the hope of obtaining further growth of pubic and axillary hair. In all other respects she seems to have achieved normal adult femininity.

#### SUMMARY

A case is reported of a 27-year-old unmarried female appearing fully 12 to 15 years younger who had had irregular scanty menstrual periods since 16 years of age, who totally lacked mammary development and axillary hair and who had but 2 or 3 hairs on the labia. She was somewhat below normal height (4 ft.  $10\frac{3}{4}$  in.); her bone age was estimated at 14 years. Slight puffiness of the features, a pulse rate of 58 to 66, a B.M.R. of  $-27\%$ , marked anemia, preference for warm weather, and easy fatigability suggested

adolescent hypothyroidism without outright myxedema.

She was treated for 1 year with thyroid substance alone, the dose being increased gradually from  $\frac{1}{2}$  grain to 2 grains daily. This not only elevated her B.M.R. to normal and diminished the anemia, but completely transformed her appearance and demeanor. Her breasts developed promptly, the menstrual periods became regular, personality became vivacious, and, in contrast to a total disinterest in the opposite sex, she married and experienced intense sexual desire and gratification.

At the end of 1 year's treatment, pubic hair remained sparse and no axillary hair had appeared. Stilbestrol (1 mg. daily, orally) was later given which seemed to stimulate additional growth of pubic hair.

The case is reported in order to draw attention to an occasional hypothyroid origin for sexual retardation. Primary deficiency of the anterior pituitary or gonads is not invariably responsible for sexual infantilism.

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# Carotinemia in Myxedema Explanation of the Typical Slightly Icteric Tint<sup>1</sup>

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## [Thyroid and Carotinemia]

IN PERUSING clinical reports of patients with myxedema, one commonly finds the color of the skin variously described as 'yellow,' 'yellowish,' 'waxy,' or 'wax-like.' Descriptive combinations, such as 'sallow-yellow,' 'yellowish pallor,' and 'slightly icteric,' are used. The pallor is easily explained by the high incidence of anemia in myxedema; but since the anemia is usually of the secondary or microcytic type, the yellowish color in the blood serum is not due to the degeneration products of hemoglobin.<sup>2</sup> In the consecutive cases presented in this paper, the 'yellowish' component invariably has been found to be due to carotinemia.

Interest in carotinemia associated with myxedema was first aroused in 1933 by a patient (case 1) with a decidedly yellowish pallor who had most of the internal manifestations of myxedema, including abdominal ascites, but few of the external signs. A marked carotinemia was found which disappeared under treatment with thyroid. The case was reported (3) and the appellation 'internal myxedema' was suggested for similar cases.

All untreated patients with myxedema seen since that time have been tested for carotinemia. In the following small consecutive series it has been present invariably. The test used was that described by Greene and Blackford (4) and Miller (5). The blood serum is mixed with alcohol and petroleum ether. Solubility of the carotin in the petroleum ether is the specific test for its presence in excess of normal.

### CASE REPORTS

Case 1, M-72835, previously reported (3). O. J., a woman aged 45, had had internal myxedema for 10 years. She showed all of the internal signs of myxedema including abdominal ascites, but few of the external manifestations. She was in the habit of eating large quantities of vegetables, and frequently carrots. Her skin was described as "pale and slightly icteric." Laboratory investigations

showed a secondary anemia, a B.M.R. of  $-37\%$ , and a plasma cholesterol of 238 mg.%. The serum carotin was 2+ with an icteric index of 15. After 8 days of treatment with thyroid and a carotin-free diet, the test for excessive carotin in the blood serum was negative. Treatment with thyroid was continued but the patient was allowed to take a normal diet. After 2 months the carotin in the serum was 3+, but after 11 months it was again negative. The Rose Bengal liver function test showed improvement after treatment with thyroid. Before treatment the 8-minute specimen showed 62% retention and the 16-minute specimen 44%; after treatment the values were 53% at 8 minutes and 32% at 16 minutes (within normal limits).

Case 2, U-15553. I. S., a woman aged 20, had developed typical childhood myxedema after an operation for 'thyroid cyst' at the age of 7. She entered the hospital because of a spontaneous abortion at 4½ months. Later an ovarian cyst with twisted pedicle was removed. No history of abnormal diet was elicited. Her height was 4 ft 6 in. Laboratory tests showed a B.M.R. of  $-25\%$ , and a plasma cholesterol of 303 mg.%. The serum carotin test was positive. The patient did not return for follow-up of endocrine therapy.

Case 3, U-17909. K. B., a woman aged 54, had typical adult spontaneous myxedema of 12 years' duration. No unusual dietary history was obtained. The skin showed a definite pallor. The B.M.R. was  $-19\%$ ; plasma cholesterol, 378 mg.%. The serum carotin test was positive. The patient responded excellently to treatment with desiccated thyroid. One and 3 months after the beginning of treatment, the test for serum carotin was still slightly positive; but after 5 months it was negative.

Case 4, U-40604. T. W., a woman aged 58, had adult spontaneous myxedema of 4 years' duration. The only deviation from the typical clinical picture was that she was somewhat thin. Her B.M.R. was  $-38\%$ , and plasma cholesterol 953 mg.%. The serum carotin test was positive. She responded well to treatment with thyroid. No further test for serum carotin was performed.

Case 5, was a patient of Dr. Fred Blake. L. S., a woman 46 years of age, had typical adult spontaneous myxedema with symptoms of 17 years' duration, which had set in after a questionable tuberculous infection following lobar pneumonia. Her skin was described as "pale with a yellowish cast." The B.M.R. was  $-45\%$ ; the plasma cholesterol, 278 mg.%. A mild secondary anemia

<sup>1</sup> Received for publication October 15, 1941.

<sup>2</sup> Aided by a grant from the Christine Breon Fund for Medical Research.

<sup>3</sup> Occasional cases of coexisting myxedema and pernicious anemia have been reported (1, 2).

present. The serum carotin test was positive. She responded well to treatment with thyroid substance. After 3½ months the serum carotin was slightly positive with an icteric index of 7.

*Case 6, U-62116. E. S.,* a woman aged 34, developed symptoms of hypothyroidism after a subtotal thyroidectomy performed 1 year previously. Her skin was described as "pale and ?icteric." The B.M.R. was -37%; the plasma cholesterol, 667 mg.%. The serum carotin test was positive and the icteric index was 15. Before treatment could be instituted, an acute psychosis developed and the patient was transferred to a psychiatric hospital.

*Case 7, 29193,* was from the clinic group of Dr. Mayo

lation concerning the relation of the carotinemia to the lowered basal metabolic rate, which was -34% in this case, is interesting. Edwards et al. (6) recently reported that carotene is present in excess in the skin of untreated human male castrates and that it diminishes to normal under treatment with testosterone propionate. A lowered B.M.R. is a frequent finding in male eunuchoidism. It usually rises to normal under treatment with testosterone.

Tests for carotinemia after treatment were carried out in 3 of the 7 cases of our series. In *case 1* the excess carotin rapidly disappeared when treatment with thyroid was combined with a carotin-free diet. How-

TABULATION OF CASES

| Case, Sex, Age, yr. | Diagnosis, Duration                           | Remarks on Color of Skin at Examination | B.M.R. | Plasma Cholesterol | Serum Carotin (Icteric Index) |                               | Thyroid Treatment, Duration        | Remarks  |
|---------------------|---|---|--------|--------------------|-------------------------------|-------------------------------|------------------------------------|--|
|                     |   |   |        |                    | Before treatment              | After treatment               |                                    |  |
| 1, O.J. ♀, 45       | Internal myxedema, 10 yr.                     | Pale, slightly icteric                  | % -37  | Mg. % 238          | +                             | Negative (8)<br>+<br>Negative | Mo. 8 days <sup>1</sup><br>2<br>11 | Internal myxedema with ascites and secondary anemia. Liver function improved with therapy. |
| 2, I.S. ♀, 20       | Childhood myxedema (after surgery when age 7) | None                                    | -25    | 303                | +                             |                               |                                    | Ht. 4 ft., 6 in. Spontaneous abortion at 4½ mo.; ovarian cyst removed later.               |
| 3, K.B. ♀, 54       | Adult spontaneous myxedema, 12 yr.            | Pale                                    | -19    | 378                | +                             | Weak +<br>Weak +<br>Negative  | 1<br>3<br>5                        | Typical case; excellent response to thyroid.   |
| 4, T.W. ♀, 58       | Adult spontaneous myxedema, 4 yr.             | None                                    | -38    | 953                | +                             |                               |                                    | Thin type of myxedema; responded well to thyroid.  |
| 5, L.S. ♀, 46       | Adult spontaneous myxedema 17 yr.             | Pale, yellowish cast                    | -45    | 278                | +                             | Weak +<br>(7)                 | 3½                                 | Onset after pneumonia and ?tuberculosis.   |
| 6, E.S. ♀, 34       | Postthyroidectomy hypothyroidism, 1 yr.       | Pale, ?icteric                          | -3     | 7                  | +                             | (15)                          |                                    | Acute psychosis developed  |
| 7, V.G. ♀, 49       | Postthyroidectomy hypothyroidism, 5 mo.       | Slightly icteric                        | -13    | 370                | +                             |                               | 2½                                 | B.M.R. before operation, +42%.   |

NOTE: One patient (*case 5*) was seen through the kindness of Dr. Fred Blake. The other patients were from the teaching services of the University of California Hospital and Clinic. One of these (*case 2*) was seen on the Obstetrics and Gynecology Service. The others were seen on the Medical Service. One patient (*case 7*) was from the clinic group of Dr. Mayo Soley.

<sup>1</sup> Carotin free diet during this period.

Soley. V. C., a woman aged 49, had post-thyroidectomy hypothyroidism of 5 months' duration. Her B.M.R. before operation had been +42%. At the time of examination, her skin was described as "slightly icteric." The B.M.R. was -13%; the plasma cholesterol, 370 mg.%. The serum carotin test was positive. She responded well to treatment with thyroid.

In addition to these cases, carotinemia was found in a patient with typical Simmonds' disease due to a craniopharyngioma (confirmed by operation). Specu-

ever, on resumption of a normal diet, the carotinemia reappeared even though treatment with thyroid was continued. After 11 months of therapy, the blood serum was again free of excessive amounts of carotin. In *case 3* the carotinemia had diminished after 1 and 3 months of treatment with thyroid and had completely disappeared after 5 months, without dietary changes. Also the patient in *case 5* was treated with thyroid alone and showed a diminished intensity of carotinemia after 3½ months.

Interest in carotinemia has been greatly stimulated by the discovery of the relationship of carotene to vitamin A. Stepp and Wendt (7) in 1937 stated that the thyroid hormone is antagonistic to vitamin A and governs the rate of its consumption. In hyperthyroidism the consumption is accelerated and the rate of change from carotin to vitamin A is increased, so that the serum carotin is low. In hypothyroidism the opposite condition is found, the vitamin A in the serum remains normal or low, and the carotin increases. These authors reported corroborative findings in a group of 11 cretins, in all of whom the serum vitamin A was low and the serum carotin was high. This observation would explain the carotinemia in diminished thyroid function whether it be of primary origin as in spontaneous myxedema or secondary to disturbed function of another member of the hormoneopoietic system as in Simmonds' disease or eunuchoidism.

Anderson and Soley (8) noted that patients with carotinemia usually show evidence of disease of the thyroid or the liver or of both. They cited the suggestion of Kerr that a primary hepatic injury could prevent the conversion of carotene to vitamin A. In support, Bessey and Wolbach (9) in 1938 stated that circumstantial evidence suggests the liver as the site of formation of vitamin A. Rabinowitch (10) in 1928 reported that the incidence of carotinemia is higher in diabetics than in normal persons. In 1936 Ralli et al. (11), after studying the effects of the administration of carotene in normal persons and in diabetics, concluded that in diabetics the liver shows a comparative inability to change carotene to vitamin A.

It seems logical to assume that a metabolic disturbance rather than an abnormality in diet is responsible for the increased incidence of carotinemia in liver disease, diabetes, and especially in hypothyroidism. In case 1, liver function by the Rose Bengal test showed marked improvement after treatment with thyroid (retention before treatment, I, 62%, II, 44%; after treatment, I, 53%, II, 32%, normal, I, 55%, II, 35%). These figures suggest that the liver also is at fault in hypothyroidism. This patient was the only one in this series who had a dietary history of unusually high consumption of carotin containing foods.

The frequent occurrence of carotinemia would seem to explain adequately the slightly jaundiced appearance that has been noted in many cases of untreated myxedema. These observations await confirmation by other investigators in larger series of cases.

#### SUMMARY

In 7 consecutive cases of untreated myxedema, co-existent carotinemia was found. It is suggested that this may be part of the typical clinical picture and may explain the 'yellowish' color of the skin so frequently observed. The carotinemia tends to clear gradually under treatment with thyroid substance.

Carotinemia was also noted in a case of Simmonds' disease, and the suggestion is made that it frequently accompanies a low B M R. The probable explanation is that the conversion of carotin to vitamin A in the liver is hindered by the depressing effect of the lowered metabolism.

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# Diagnosis of Addison's Disease

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## [Addison's Disease]

WITHIN RECENT YEARS the older practice of administering desiccated endocrine glands, as a means of substitution therapy in various endocrine disorders, has been replaced largely by the use of specific hormones, hormone-like compounds and related chemotherapeutic agents. With the exception of the thyroid gland, desiccated organs are now known to have little therapeutic value other than a psychologic influence or as a placebo.

Physiologically active endocrine products and synthetic chemical substances are becoming available in rapidly increasing numbers. Their medicinal values, however, are not always adequately established before they are in general use as therapeutic agents. It appears that the therapeutic value of some products is not infrequently overestimated, which may be the result of relying on questionable criteria for determining supposed benefit. In some instances this is obviously due to mistaken diagnosis, whereby alleged benefit of treatment can be explained by an improvement which was not related to the administration of a specific remedy.

In the case of Addison's disease, the foregoing suggestion seems particularly pertinent. During the past 15 years renewed interest in this disease has been stimulated by the development of a more promising type of therapy. The increased number of cases reported in the literature almost suggests a greater incidence of the disease. Because of the relative infrequency of this condition, it seems possible that some cases might have been mistakenly diagnosed. In such cases any therapy may be followed by more striking improvement than usually occurs in well defined Addison's disease and undue confidence in the specific medication employed may result.

The reports in the literature indicate that a diagnosis of Addison's disease is often made on an inadequate clinical basis, and that some genuine cases escape proper diagnosis during the life of the patient. This is not surprising since Addison's disease is not a

common ailment. It seems useful, therefore, to record any information which may aid in the recognition and in the treatment of this disease. Experimental investigations on the physiology and pathology of the adrenal glands were begun 25 years ago in collaboration with the late Professor G. N. Stewart, and have led to the study of Addison's disease as a corollary to those researches. In the present summary of these observations, clinical interpretations are based on the results of the experimental as well as clinical investigation.

In uncomplicated cases, diagnosis of Addison's disease usually can be made with reasonable certainty. The classical description of the syndrome, published in 1855 by Thomas Addison (1) includes the combination of symptoms that characterizes the disease. Briefly, this is an association of persistent gastrointestinal disturbances, progressive circulatory and muscular asthenia, and a peculiar discoloration of the skin. If not accounted for otherwise, occurrence of these associated symptoms should suggest Addison's disease.

Usually the disease escapes early recognition and effective treatment, and a subacute exacerbation or an acute crisis develops within a few months from the onset of these symptoms. In untreated cases, or in those in which there is severe and extensive bilateral degeneration of the adrenal cortex, a fatal outcome is inevitable within 1 to 2 years from the period of onset of the related symptoms. Death may occur in consequence of the first acute crisis, more commonly the second and occasionally the third. A notable characteristic of Addison's disease is the occurrence of a more or less abrupt remission during a subacute exacerbation or, not infrequently, from acute crisis.

Most cases of Addison's disease present sufficient criteria for diagnosis. Attempts to precipitate a crisis by depriving the patient of salt or by administering toxic amounts of potassium are too risky if the condition is so far advanced as to suggest the presence of Addison's disease. If a diagnosis of Addison's disease is under consideration and if it is suspected that adrenal cortical degeneration is moderate in extent and is early, then a therapeutic test by administration of interrenalin and saline as a diagnostic aid seems

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justified. The reliability of such a test may be subject to question, yet it is safer than the practice of risking life by the dangerous procedure of inducing an acute crisis in a true case of Addison's disease.

In previous reports (6) certain aids in diagnosis have been presented. These are: a) aversion to fat in the diet, b) the reaction to costo-lumbar pressure, and c) changes in the blood comparable with those observed in experimental animals with adrenal cortical insufficiency. Aversion to fats was found, almost invariably, in bilaterally adrenalectomized dogs shortly before the onset of anorexia (7). It is suggested that this may be related to the marked congestion of the pancreas that occurs in these animals. Congestion of the pancreas, has been observed at autopsy in cases of Addison's disease, especially when adrenal degeneration was severe and rapid, and the patient had succumbed in the first acute crisis, inquiry commonly reveals that aversion to fats developed at the time anorexia first became evident. Patients often state that fatty foods induce nausea or diarrhea, whereas prior to the onset of the illness, fats were well tolerated and in some instances were preferred in the diet.

The costo lumbar pressure reaction, referred to as Rogoff's sign (3), is elicited by moderate pressure with a finger in each costo-lumbar angle. The test is performed with the patient lying flat on the back, completely relaxed. The examiner's hands are placed under the patient so that the index or middle finger rests in the costo lumbar angle on each side. Moderate pressure is exerted with the fingers, in a forward inward upward direction. On the left side the reaction may be obtained more readily if the finger is placed about  $\frac{1}{2}$  of an inch below the angle and on the right side well up in the angle. If there is active degeneration of the adrenal gland this procedure elicits a dull pain or aching sensation, usually the discomfort is local. If active inflammation, marked edema, or extensive caseous degeneration of the adrenal is present the sensation is not only local but often is referred toward, but not into, the pelvis of the affected side. These observations have been confirmed by correlating clinical with autopsy findings. Usually, the reaction can be demonstrated easily during acute or sub acute exacerbations. As repair or regeneration of the adrenal ensues the sign becomes less definite and may finally disappear until another exacerbation occurs.

If the reaction has been present on repeated examinations during a period of some months, and then disappears entirely, while the condition of the patient declines, it can be assumed that the adrenal gland has undergone practically complete degeneration. This has been revealed, repeatedly, at autopsies in cases without gross evidence of associated tubercu-

losis. Caseous degeneration of the adrenal is commonly associated with clinical evidence of the existence of active or latent tuberculosis elsewhere. Often, calcareous deposits may be detected by roentgenography. These may occur without development of Addison's disease, in such a case the disappearance of the reaction may indicate healing of the gland by calcification, fibrosis, or both.

The clinical significance and value of the costo-lumbar sign is illustrated by the protocols of 2 cases, which follow. In one, a blonde woman without the characteristic skin pigmentation was in acute Addisonian crisis, diagnosis was unquestionably facilitated by relying on this sign. The second case illustrates the advantage of the sign as an index of gradual adrenal damage up to practically complete degeneration.

*Case 1, E. H., housewife, 33 years old.* Patient was admitted to hospital in acute condition on Aug. 31, 1930. *History.* Family Father, accidental death, age 58 yr., mother, 67 yr., stomach trouble, 2 sisters, both sickly. No history of tuberculosis. *Personal.* Previous health generally fair, except as follows. About 5 years ago became "almost blind" for a while, as the result of the shock of her father's accidental death. Since then, has had frequent headaches, occasional cough. No evidence of cardiac weakness, appetite variable, bowel function irregular, blood in stools once about 5 yr. ago. Nocturia, 1 to 2 times nightly since marriage. Menses always irregular, duration 3-5 days, 1 pregnancy. Male child 5 years old. *Present illness.* For years has complained that feet get cold easily, no tingling sensation. In past 2 months has felt weak, tired easily and has slowly lost weight. Menses ceased 9 months ago, menstruated only once since, last month, 3 days flow. Last winter she had what was diagnosed as "grippe", had a cold in chest and slight cough, no blood. For the past 6 weeks she had been repeatedly "excited and frightened" over some domestic troubles.

Five weeks ago, ate some green apples which caused epigastric pain, no diarrhea or vomiting but some nausea, no fever. Since then she has felt very weak, fatigue and loss of weight have been progressive. Edema of ankles occasionally during past 2 years. *Physical examination.* Patient is somewhat emaciated. Excitable during examination. Head, eyes, nose, ears, normal. Mucosa of mouth, cheeks and tongue, pale. Thyroid barely palpable. Chest findings normal. Heart sounds weak, regular, rhythmical, no murmurs. Abdomen had slight tenderness in epigastrium and about the umbilicus. Genitalia and pelvis normal. A provisional diagnosis of pernicious anemia? Cancer? was made by the House Staff.

9/1/30 very weak and nervous. 9/2/30 condition unchanged, nauseated. 9/3/30 nausea and cramps in stomach, cyanotic, pulse cannot be felt, extremely weak, B.P. 60/40, hypotension unexplained. B.P. 60-65/20, suggests diagnosis of early Addison's disease, or hemorrhage into

<sup>1</sup> Courtesy of Staff, Cleveland City Hospital, Cleveland, Ohio. Abstract of hospital record.



adrenals. 9/4/30: roentgenogram shows evidence of old (fibrous) tuberculosis scar in apex of left lung. E.K.G., normal mechanism; inverted T leads 2 and 3. Icteric index 10. Temperature chart normal. 9/5/30: patient pulseless, could not get blood pressure. Administered 0.5 cc. of adrenalin in saline, intravenously; followed by blanching of mucus membranes, nausea and dyspnea. 9/6/30: saline-glucose (5%) administered; introduced 3 minims adrenalin via needle in rubber tube and patient had same reaction as mentioned above; no more adrenalin employed.

*Consultation note (J.M.R.).* History and clinical condition do not support diagnosis of cancer. Pernicious anemia ruled out by blood examination. Roentgenogram of chest shows latent tuberculosis. Two small areas of pigment in mucosa of right cheek and a small one in right angle of lips.

The patient is blonde, therefore, absence of skin pigmentation is not significant. Rogoff's sign present on both sides but decidedly more marked on right side. This would indicate bilateral adrenal degeneration, with more extensive or more recent degeneration of the right gland.

a) The clinical condition of the patient, b), history of latent tuberculosis, confirmed by X-ray plate of chest, c), presence of costo-lumbar pressure sign, d), low blood-pressure (acute crisis), e), marked asthenia, f), gastro-intestinal disturbance, g), moderate decrease in blood sugar and h), increase in N.P.N. with moderate increase in urea N, support the diagnosis of Addison's disease. Prognosis very grave; repeated intravenous saline-dextrose and interrenalin was recommended although it appeared unlikely that patient could survive beyond a week.

9/10/30: patient somewhat improved; ate meal with fair appetite. 9/11/30: declining; irrational; pulse imperceptible. 9/12/30: patient died, midnight. 9/13/30: Autopsy, 10 A.M., complete except for brain and cord.

*Abstract of notes.* Adrenals: The glands could not be identified until the vena cava was opened, the orifices of the adrenal veins identified and a probe was passed up into the veins and left in situ. The kidneys and surrounding tissues, up to the diaphragm and for about the same distance below the kidneys, were then removed, en masse, including corresponding portions of the aorta and vena cava. Carefully dissecting away adjacent fat, the atrophic remains of the adrenals were found. Both glands presented only the fibrous capsule containing a little bluish debris in which was seen a small yellowish streak about 1 to 2 mm. thick and about 8 mm. long in the left and less in the right. The bluish debris was more marked in the right. Adrenal veins patent.

*Microscopical description.* In both organs, the parenchyma, including the medulla, was replaced by edematous, loose areolar tissue containing numerous scattered foci and few localized areas of small round cells resembling lymphocytes. There were large areas of free hemorrhage beneath capsule. Scattered clumps or rows of 2 to 5 cells in syncytial-like arrangement with amphophilic cytoplasm and small round nuclei represented degenerated cortical cells.

*Pathological diagnosis:* Addison's disease with severe atrophy of adrenal glands, bilateral; fibroid tuberculosis, left upper lobe; congested pancreas; hypertrophied lymphoid tissues, intestines.

Case 2, L. G., housewife; 28 years old.<sup>3</sup> 11/26/27. Pa-

tient seen in consultation with Dr. Pearce, at Akron Clinic. *History.* Family. Father, mother, 2 brothers, 3 sisters, all living and well. Personal. Married 2 years, no children; no miscarriages. Whooping cough, measles and scarlet fever in childhood. Menses began at 15 to 16 yr.; generally regular up to present; flow scanty, fair for one day and slight for nearly a week. About a year ago, contracted tonsillitis which confined her to bed for about 2 weeks, this was associated with severe backache; has never felt well since this illness. Developed persistent fatigue. A few months later, in the spring of 1927 she noticed pigmentation of skin on face and hands; fatigue on slight exertion; nausea and vomiting developed. Gradual loss of weight since then. *Present illness.* Patient complains of nausea and frequent bilious vomiting, lassitude and increasing muscular weakness; increasing pigmentation and backache; appetite fair but has aversion to certain articles of diet, especially fats; no cough or night sweats although these had been present formerly. *Physical examination.* Patient uniformly pigmented with accentuation in areas normally pigmented; pigmentation over joints, and surfaces on which pressure of garments is common, also in scars. No pigmentation in mucosa of mouth or tongue. No epigastric pain, but tenderness over epigastrium on pressure, which induces nausea. Mass is felt in lower abdomen on the right side extending from the pelvis upward to below umbilicus. Pulse rapid with excitement. Blood pressure 120/90 mm. Hg. at first but as patient overcame excitement due to examination the pressure declined (in 20 minutes) to 96/60 mm. Hg. Later, it declined to about 85 systolic. Costo-lumbar index (Rogoff sign), right ++, left +.

Tonics and adrenalin, had been used and were continued for a while, but without benefit. 3/6/28: Condition poor; gastro-intestinal disturbances; asthenia; blood pressure 78/60; costo-lumbar index, right ++, left ++. Treatment with interrenalin, by mouth, begun. This was continued for nearly 4½ years throughout the period of survival of the patient to 7/22/32. Occasional intravenous injections of saline-dextrose solution were given as required. Within 2 weeks, her condition improved remarkably. Systolic blood pressure rose and was sustained at about 114 mm. Hg. The patient gained in weight and strength, and was able to resume household duties, which she had been forced to give up; also engaged in social and other activities. An interesting observation is that the menstrual flow was more normal since treatment with interrenalin was begun, and that the patient's condition seemed better during the menstrual periods than at any other time.

During the progress of the case, she had 3 or 4 subacute exacerbations requiring increased dosage of interrenalin and more frequent saline-dextrose injections. These exacerbations appeared to be directly related to overactivity up to the point of fatigue, and in one instance resulted from a long automobile trip. In October, 1929, she had an acute crisis in which the blood pressure fell to about 60 mm. Hg. systolic. There was nausea and vomiting (bile); extreme

<sup>3</sup> Courtesy Dr. R. G. Pearce, Akron Clinic, Akron, Ohio. Abstract of record.

asthenia, costo lumbar index ++ on both sides Treatment was followed by decided improvement within a week

The costo lumbar index was always more easily elicited and yielded a greater response during each exacerbation As improvement occurred, it became less marked on both sides It disappeared and returned a number of times on the left side, and finally disappeared entirely During the last year of her survival the C-L observations were as follows 6/28/30, right ++, left -, 9/13/30, right +, left -, 3/30/31, right ++, left +, 10/18/31, right ++, left +, 1/29/32, right -, left -, 5/12/32, right +, left -, 7/21/32, right -, left -, Died, 7/22/32

7/22/32 Autopsy, complete except for brain and cord (Courtesy of Dr D P Seccord) Abstract of notes adrenals Right In its situation is found an area 2 cm in diameter, of highly vascularized fatty tissue containing small yellowish white and purplish black nodules some of which are as large as 2 mm in diameter These nodules within the fat are contained within a roughly triangular region suggesting the outline of the original gland The measurements of this region are  $5 \times 5 \times 2$  mm in the form of an isosceles triangle in which the 2 mm represents the base The vein cannot be identified At the vena cava the orifice is identified but the lumen is occluded Left Is identified as a small, roughly bean-shaped nodule measuring  $2 \times 1 \times 5$  cm Externally it appears to be made up of a purplish black tissue similar to that described as nodules for the right In association with this gland, however, the main vein is identified and traced down to its junction with the renal vein over a distance of 2 cm, until it is lost within the depth of this nodule it appears normal

*Microscopical description* Right (1) Contained within areolar fatty tissue is a small globular mass completely encapsulated This mass is made up of very large, somewhat irregular cortical cells with heavily staining cytoplasm and irregular bizarre nuclei The irregularities of the nuclei vary from pyknosis to vesicle formation and ring forms The cells show no definite architectural arrangement They are irregularly distributed and separated by thin vascular connective tissue septa Within the latter are large foci of round cell accumulation At one pole of this globular cortical mass there is an adherent layer of fibrous tissue, at one place containing a vessel with a well defined lumen External to the endothelium of this vessel there are collections of round cells (2) Elongated piece of tissue, the greater portion of which is made up of areolar fatty tissue containing small islands of 'glandular fat' On one surface of this fatty tissue is the remains of an adrenal composed for the most part of a thickened fibrous capsule and containing in its central portion fairly normal veins At irregular intervals throughout this structure are small collections of cortical cells alternating with medullary cells, measuring not over  $100 \mu$  The latter appear intact, the former, similar to those in section 1, are irregular and show no architectural arrangement There are foci of round cells scattered throughout the tissue In this section, tubercle bacilli found (3) Essentially similar to section 2 except that the cortical and medullary masses are larger and well preserved In this section also there is a small nodule of cortical tissue retaining somewhat the nor-

mal histological arrangement In this section the medulla is well preserved, the round cell infiltration more marked In places the round cells form the only cellular content between the layers of the capsule

Left (1) The outline of the section is triangular, suggesting the normal gland The capsule is thickened, and contains nodules of cortical cells, irregular in size, staining reaction nuclear content and histological arrangement, the entire picture suggesting regenerated and degenerating cortical tissue In this section there is no medulla The central veins are in apposition with the cortical cells (2) Globular mass of cortical tissue showing in places the architectural arrangement of the normal gland a fairly well defined glomerular and fascicular layer For the most part, however, the cortical cells are irregularly arranged on a thin vascular stroma Here and there are small foci of large irregular cortical cells with irregular nuclei Immediately adjacent to this mass is a large blood space lined by a thin fibrous wall adjacent to what appears to be the remains of the normal gland as indicated by the veins About the latter are a few small medullary masses and collections of round cells At a distance from the cortical mass is a sympathetic ganglion mass showing no abnormalities (3) No adrenal tissue recognized Adjacent to the large renal vein are lymphoid masses showing slight endothelial hyperplasia and congestion Within the areolar fatty tissue about these structures are small areas of glandular fat

*Pathological diagnosis* Addison's disease with extensive atrophy of adrenals, ('cytotoxic') bilateral Pigmentation of skin and mucous membranes, lymphoid hyperplasia in colon, pulmonary emphysema, slight, atrophy parenchymatous organs, healed tuberculous focus, hilum of left lung, fibrous thickening of mitral leaflets, peritoneal adhesion, right iliac fossa, lymphorrhagia of pancreas, thyroid, parathyroid, voluntary muscle, focal necrosis of germinal centers of lymphoid follicles

*Pathology.* Absence of active or latent tuberculosis in a case of Addison's disease, with progressive degeneration of the adrenals as evidenced by repeated presence and ultimate disappearance of the costo lumbar sign, suggests existence of the so-called 'schrumpfbrenniere,' or 'cytotoxic atrophy' I believe that this type of degeneration also is due primarily to tuberculosis rather than to the suggested action of a specific cellular toxin (Case 2) Careful search commonly reveals the presence of a Ghon lesion in the lung or sub-pleural region This may have undergone caseation or, more often, it has healed by calcification, sometimes by ossification In case 2 (6, case 3, table 1) serial section of the minute remnant of atrophic cortical adrenal tissue found at autopsy revealed the presence of tubercle bacilli There was no caseation or calcification of the adrenals

The suggestion can be made that the tubercle bacilli, may not cause caseous degeneration in some cases but might be responsible for liberation of a toxin that destroys the cells of the adrenal cortex However, if this were true it would have to be assumed that the

organism must be located in the adrenal to produce such a result. Otherwise, tuberculosis outside of the adrenal should be capable of producing the cytotoxin and Addison's disease would be an almost constant sequel of chronic tuberculosis. It seems more probable that presence of the micro-organisms in the adrenal results in pathologic processes that involve the adrenal blood vessels which then become partly or wholly occluded. Such interference with the circulation can lead to local ischemia, anemic infarction and cellular degeneration with resulting atrophy and fibrosis. Adequate collateral circulation may lead to some regeneration which, co-existing with the degenerative process, yields the characteristic pathology found in 'schrumpfnenniere.'

By subtotal occlusion of the adrenal blood vessels, it has been possible to create subacute and chronic adrenal cortical insufficiency experimentally in animals in which examination of the adrenals at autopsy revealed the typical picture of the adrenal described as cytotoxic atrophy (8). The clinical manifestations and blood changes, as well as the pathologic appearance of the adrenal glands in these animals were similar or identical with observations in comparable human cases of Addison's disease. The blood changes that occur in experimental animals with subacute or chronic adrenal cortical insufficiency, are similar to but less marked than those which occur in experimental acute adrenal insufficiency induced by total adrenalectomy (9).

**Blood changes.** During acute and subacute exacerbations there is an elevation of the total N.P.N. In a severe crisis the urea N also increases but not enough to account for the rise in total N.P.N. The significant change is reflected in an elevation of the so-called 'undetermined fraction' of the N.P.N. This escapes notice if the common practice is to determine only one of these factors. For example, in case 20 (6) chemical examination of the blood performed for diagnostic confirmation revealed the level of urea nitrogen as 18 mg.%, which was within the normal range, while the total N.P.N. was found to be 52 mg.%, decidedly above the upper limit of the normal range. Similar instances have been observed, repeatedly. Total blood calcium usually is elevated in subacute and acute stages of adrenal cortical insufficiency.

The blood chlorides are diminished. This has been attributed to excessive excretion through the kidneys. Loeb et al. (5) observed that the diminution of blood chlorides is associated with a loss of sodium from the body, suggesting a regulatory rôle of the adrenal cortex in relation to Na metabolism. There is evidence in support of the retention of K associated with the loss of NaCl from the blood. In view of the generally recognized fact that available microchemical quantita-

tive methods for estimation of K in the blood are unsatisfactory, this will bear more adequate confirmation. It must be remembered, also, that some of the chemical changes in the blood which occur in consequence of the severe disturbances that are associated with an acute crisis may be secondary to those disturbances and not primarily related to Addison's disease.

A number of authors have emphasized hypoglycemia as a constant manifestation in Addison's disease. This view appears to have originated from observations on adrenalectomized animals that survived for only a short period (2). During the period of survival of untreated adrenalectomized dogs, the blood sugar level rarely declined below the lower limit of the normal range, in animals that survived longer, until a moribund condition developed (9). Definite hypoglycemia appears to be associated only with serious complications and not with loss of adrenal function. The same observations apply in the case of human Addison's disease. In severe crisis, when hemoconcentration occurs, blood chemical changes that are usually found may be considerably modified. This is especially true in the moribund state.

**Pigmentation.** Addison described a characteristic pigmentation of the skin, to which he referred as 'bronzing.' This pigmentation generally can be distinguished from that which occurs in conditions other than Addison's disease. It may be described as a mixture of various shades of tan with slate grey, usually having a dull, dry, 'dirty' appearance. Many writers on Addison's disease have relied on pigmentation of the skin as pathognomonic. In fact, a relatively large proportion of the cases that have been reported within the past decade have little more than the incidence of this symptom to support the diagnosis. Diminished pigmentation often has been reported to follow treatment. Usually this is only apparent and merely indicates improved circulation during the period of better health of the patient. Occasionally, however, a moderate degree of actual reduction in the amount of pigmentation may occur in those patients that respond well to treatment and survive in fairly good condition for a relatively long period.

Although pigment deposit in the skin and mucous membranes occurs in the classical picture of Addison's disease, it is not pathognomonic unless it is associated with the other definite symptoms described previously. It has been pointed out in other publications (6), that Addison's disease not infrequently occurs with little or no pigmentation of the skin, the diagnosis in such cases having been confirmed at autopsy. In negroes, it is often difficult to detect the additional pigmentation of the skin. Pigment deposit may be found in creases of the skin in the palms of the

hands and the soles of the feet. Another location is in the buccal mucous membrane.

In the cases observed, complete or nearly complete absence of skin pigmentation has occurred only in blonde individuals (case 1). Furthermore, it was found that such cases are much more resistant to treatment and that they have a more rapidly fatal outcome. As a general rule, prognosis of a fatal outcome within approximately a half year from the onset of definite symptoms of adrenal cortical insufficiency, has proven correct in blondes. Even if treatment is more effective in some cases, it appears that life can not be prolonged for more than about another  $\frac{1}{2}$  year. Where autopsy was performed in cases of this type, extensive atrophy with or without associated fibrosis of the adrenals was found. Addison's disease, when due to tuberculous (caseous) degeneration of the adrenals in blonde individuals appears to be more chronic than when it is due to adrenal atrophy, and usually it is associated with pigmentation of the skin.

In the more severe cases of Addison's disease, especially in those associated with atrophic degeneration of the adrenals, small, rounded, freckle like, ebony-colored spots often appear on the neck, shoulders, arms and forearms, sometimes on the back and chest. Occasionally, they constitute the only evidence of pigmentation. Their presence and progressive increase in number and points of distribution apparently indicates an advanced stage of the disease, since it was observed that most cases terminated fatally within a few months after the appearance of these ebony colored spots, particularly in decidedly blonde patients.

**Differential diagnosis.** The principal source of difficulty in differential diagnosis appears to arise from the fact that pigmentation of the skin is the chief, if not the only symptom commonly relied on to determine the diagnosis of Addison's disease. Certain other diseases, associated with pigmentation, have been confused with Addison's disease, such as chronic tuberculosis, melanotic dermatoses, chronic thyroid disease, hemochromatosis or diabète bronzé, neurocirculatory asthenia in persons with dark complexion, and chronic poisoning with certain metals.

It should not be difficult to distinguish between chronic hypothyroidism and Addison's disease, especially in cases reported with a history of surgical removal of the thyroid (4). Reduction of the basal metabolic rate has been relied on, by some observers, as a significant symptom of Addison's disease. While some cases present a slight reduction, others have an elevation of the B M R. In acute crisis of Addison's disease the B M R. may decline to a level comparable with that which occurs in hypothyroidism, but these two conditions can hardly be confused if the usual criteria for differential diagnosis are observed.

Real difficulty sometimes arises in distinguishing Addison's disease from chronic tuberculosis without adrenal involvement or with minor adrenal degeneration. Muscular and circulatory asthenia, pigmentation of the skin, and gastro intestinal disturbances often are associated with tuberculosis. Since this disease is the most common etiologic factor in Addison's disease, differential diagnosis may not be easy. In such a case the costo lumbar sign is of particular value. A positive reaction is elicited, almost invariably, when active and extensive caseous or hyaline degeneration of the adrenal exists. In the presence of tuberculosis elsewhere this would confirm the probability of existence of Addison's disease. Absence of the reaction would suggest that the adrenals are not involved. As previously indicated, however, tuberculous degeneration may occur in part of the adrenal, in the course of generalized tuberculosis, without leading to Addison's disease. Such degeneration when limited in extent may heal by calcification or fibrosis with improvement in the patient's general condition. If this occurs the costo-lumbar sign may be present during adrenal degeneration and absent when degeneration has subsided. In such a case, absence of the usual blood chemical changes at the time when the costo lumbar sign is present, complete disappearance of the sign later, and improvement of the patient would indicate that diagnosis of tuberculosis rather than Addison's disease is more probably correct.

Roentgenologic evidence of calcareous deposits in the adrenals, in cases of tuberculosis elsewhere, without other definite symptoms of Addison's disease, more commonly indicates healing of a pre-existing degenerative process in the glands rather than the presence of Addison's disease. Of course, recurrence of degeneration and ultimate development of Addison's disease can and undoubtedly does occur in some of these cases, and the patient again yields a positive costo lumbar sign until complete degeneration (or regeneration) of the gland takes place. However, the mere presence of a calcified area in the adrenal region, revealed by roentgenography in a patient with latent tuberculosis, does not suffice to establish a positive diagnosis of Addison's disease. Such patients may live for years without manifesting any of the unmistakable evidences of serious adrenal cortical insufficiency. Unless other symptoms occur, the diagnosis ought to be limited to tuberculosis, though keeping in mind the possibility of ultimate development of Addison's disease. It may be mentioned that calcified areas are found frequently in the adrenals of normal experimental animals and in glands obtained from the abattoir.

This type of case can explain statements that have been made to the effect that some patients with Addison's disease have survived for many years.

organism must be located in the adrenal to produce such a result. Otherwise, tuberculosis outside of the adrenal should be capable of producing the cytotoxin and Addison's disease would be an almost constant sequel of chronic tuberculosis. It seems more probable that presence of the micro-organisms in the adrenal results in pathologic processes that involve the adrenal blood vessels which then become partly or wholly occluded. Such interference with the circulation can lead to local ischemia, anemic infarction and cellular degeneration with resulting atrophy and fibrosis. Adequate collateral circulation may lead to some regeneration which, co-existing with the degenerative process, yields the characteristic pathology found in 'schrumpfnenniere.'

By subtotal occlusion of the adrenal blood vessels, it has been possible to create subacute and chronic adrenal cortical insufficiency experimentally in animals in which examination of the adrenals at autopsy revealed the typical picture of the adrenal described as cytotoxic atrophy (8). The clinical manifestations and blood changes, as well as the pathologic appearance of the adrenal glands in these animals were similar or identical with observations in comparable human cases of Addison's disease. The blood changes that occur in experimental animals with subacute or chronic adrenal cortical insufficiency, are similar to but less marked than those which occur in experimental acute adrenal insufficiency induced by total adrenalectomy (9).

**Blood changes.** During acute and subacute exacerbations there is an elevation of the total N.P.N. In a severe crisis the urea N also increases but not enough to account for the rise in total N.P.N. The significant change is reflected in an elevation of the so-called 'undetermined fraction' of the N.P.N. This escapes notice if the common practice is to determine only one of these factors. For example, in case 20 (6) chemical examination of the blood performed for diagnostic confirmation revealed the level of urea nitrogen as 18 mg.%, which was within the normal range, while the total N.P.N. was found to be 52 mg.%, decidedly above the upper limit of the normal range. Similar instances have been observed, repeatedly. Total blood calcium usually is elevated in subacute and acute stages of adrenal cortical insufficiency.

The blood chlorides are diminished. This has been attributed to excessive excretion through the kidneys. Loeb et al. (5) observed that the diminution of blood chlorides is associated with a loss of sodium from the body, suggesting a regulatory rôle of the adrenal cortex in relation to Na metabolism. There is evidence in support of the retention of K associated with the loss of NaCl from the blood. In view of the generally recognized fact that available microchemical quantita-

tive methods for estimation of K in the blood are unsatisfactory, this will bear more adequate confirmation. It must be remembered, also, that some of the chemical changes in the blood which occur in consequence of the severe disturbances that are associated with an acute crisis may be secondary to those disturbances and not primarily related to Addison's disease.

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# Treatment of Addison's Disease with Interrenalin (Adrenal Cortex Extract)

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## [Addison's Disease]

THE FIRST DEMONSTRATION that active endocrine material can be extracted from the adrenal cortex, and that it is capable of prolonging life and mitigating symptoms in completely adrenalectomized animals, was by Rogoff and Stewart (1) in 1925. Their experimental observations constitute the basis for the method that is now generally employed in the treatment of Addison's disease. The first demonstration that substantial benefit may be derived from administration of potent adrenal cortex extract, in Addison's disease, was published by the same authors (2), in 1929. Amelioration of symptoms was the outstanding observation in 7 patients that had been under treatment with interrenalin,<sup>2</sup> in the form of an extract of adrenal cortex, for periods ranging from approximately 6 to 18 months.

Other articles (3), were followed by a second report (4), in 1932, which included 14 additional cases together with further observations on the original 7. It was clearly shown, by comparison with a control group of 12 cases, that substitution therapy with interrenalin not only caused relief of symptoms but prolonged life in a large proportion of the treated cases. Further clinical experience with Addison's disease and continued experimental animal investigations on adrenal insufficiency warrant publication of another report concerning this method of treatment.

During the past 15 years, observations have been made on patients with Addison's disease treated by the method which originated from the investigations on adrenal insufficiency and its correction in experimental animals. This consists of administration of interrenalin, with or without supplementary intravenous injections of physiologic salt solutions. In 1925, it was demonstrated that completely adrenalectomized animals can be kept alive and well for relatively long periods, if potent adrenal cortex extracts, or physiologic salt solutions, are administered (1). Treatment with both resulted in much longer survival, suggesting clinical trial of the same treatment, in Addison's disease.

At present, the most that can be expected from the best available method of treatment in Addison's disease is a substantial prolongation of life with mitigation of the severity, and reduction in the frequency of recurrence of aggravating symptoms. This is obvious from available knowledge of the pathologic anatomy and physiology of the adrenals in this disease, as well as from proper evaluation of the results of treatment. Substitution hormone therapy does not eliminate the underlying cause of adrenal degeneration. Indirectly, by increasing the patient's resistance, this therapy might retard the pernicious influence of the etiologic factor, thus favoring regeneration in the adrenals. However, it cannot wholly remedy that serious factor.

In general, Addison's disease at present must be considered as an incurable and ultimately fatal malady. It is conceivable, though probably hypothetical, that rarely a benign etiologic factor might induce moderate degenerative processes in the adrenals and lead to development of a less severe form of Addison's disease. If such a benign factor were responsive to treatment, or if it subsided spontaneously, adequate substitution therapy might be followed by adrenal regeneration or by cessation of degeneration. This could result in healing of the damaged adrenals, effecting a clinical 'cure'.

Two patients that possibly may be classed among such cases have been observed. However, on strictly scientific premises, it must be admitted that although the clinical diagnosis of Addison's disease was inescapable on the basis of all the determining factors known, there is nevertheless the possibility that the diagnosis could have been an error. This unavoidable conclusion must govern all interpretations that are made regarding the evaluation of any particular therapy.

Formerly, treatment of Addison's disease was based on the assumption that this malady is the result

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<sup>2</sup> Interrenalin is a name employed by various manufacturing firms for commercial adrenal products.

of functional insufficiency of the adrenal medulla, that is, inadequate epinephrine secretion. That is the basis for the so-called 'Muirhead treatment.' This has been discarded by clinicians generally since it is well established that epinephrine secretion from the adrenals is not essential for life and health (5). The indispensable function of the adrenals is performed by interrenalin, the adrenal cortical hormone. Insufficiency of cortical function is responsible for the serious consequences that occur in Addison's disease. In creating experimental Addison's disease in animals selective degeneration of the cortex commonly occurs while the medulla remains intact (6).

Administration of adrenalin has proven to be of little if any value in Addison's disease. Indeed, it has been observed, frequently, that attempts to elevate the blood pressure by administration of adrenalin, or ephedrin, cause distress and alarming cardiac reactions (7, case 1). This is not surprising, since cardiac degeneration with atrophic changes is often revealed at autopsy in Addison's disease. In one instance, the heart weighed only 98 gm. Such a heart can not be expected to sustain a greatly elevated blood pressure without functional embarrassment. Nor is it necessary to assume that 80 to 100 mm. Hg is not adequate blood pressure for functional needs of a patient with Addison's disease, who is otherwise maintained in fairly good condition.

Some clinicians have administered pituitary gland preparations for Addison's disease. The use of desiccated gland, by mouth, scarcely needs comment. It is well known that the pituitary is inactive when given in this manner. Others have thought that an extract of pituitary might be useful, presumably on the assumption that an adrenotropic or interrenaltropic action would be beneficial. Even if it were established that adrenal cortical function is dependent on interrenaltropic pituitary activity, it does not seem probable that adrenals which have undergone and are in active progress of serious, extensive degeneration, could respond adequately to such stimulation of function. There is evidence that the interrelated activity between the adrenals and the pituitary probably is not at all concerned with the indispensable adrenal cortical function (8).

Results of treatment in Addison's disease can be evaluated best if they are related to the known physiology and pathology of the adrenals. Various theories have been proposed to explain the function of these glands, particularly the cortex. Among these are regulation of a) electrolyte balance, b) water balance, c) carbohydrate metabolism and d) blood pressure. There is no good reason to accept any one of these individual explanations. Changes occur in all of these factors in various phases of adrenal cortical insufficiency. All of them are included in the entire dis-

turbance. It seems preferable to retain our original view that the adrenal cortex performs an indispensable metabolic function, failure of which is manifested by a severe functional disturbance in which each of these factors participates. The complete picture is one of a profound intoxication following disrupted metabolic regulation.

Accordingly, treatment of Addison's disease is directed toward combating three major factors, a) etiologic, b) pathologic and c) physiologic. In the majority of cases, treatment of the etiologic factor is that of tuberculosis. Insofar as this disease may or may not be responsive, such treatment will determine the progress of the pathologic factor concerning the adrenals. If active degeneration can be retarded, regeneration may be favored by supplying the hormone which the adrenal must elaborate and secrete to sustain life and improve health. The physiologic factor involves not only supplying interrenalin, which the adrenal is incapable of elaborating properly, but also correction of the pathologic physiology that exists in consequence of functional lack of this hormone. Since the symptoms indicate retention of toxic metabolites, dilution and elimination of these may be facilitated by appropriate intravenous administration of physiological liquids.

It was demonstrated (4) that this treatment is capable not only of ameliorating symptoms but that it can effect a decided prolongation of life, if complicating etiologic factors are not rapidly fatal. Some patients were given interrenalin alone, others intravenous injections of salt solutions alone, and most of them received both. Survival for 8 or more years from the time of onset of the disease has occurred in cases where the clinical diagnosis of Addison's disease was beyond question. Two patients, under present treatment with interrenalin, have continued in very satisfactory condition for more than 8 and 4½ years, respectively. Clinical diagnosis in these cases can not be disputed.

Addison's disease was recognized in the first<sup>3</sup> of these cases when an acute crisis followed herniotomy. In the second case, the patient had received a commercial adrenal product (eschatin), parenterally, salt tablets orally, and was on a restricted diet limiting potassium intake for more than a year, without benefit. He was declining rapidly when administration of glycerinated solution of interrenalin alone, by mouth, was begun. This treatment was continued, with marked benefit up to the present. Recently the synthetic drug desoxycorticosterone-acetate was substituted for the adrenal cortex extract that he had been receiving. He suffered a decline in his general

<sup>3</sup> I am indebted to Dr. S. Berger and other members of the staff of Mt. Sinai Hospital, Cleveland, who referred this case to me for observation and treatment.



condition and blood pressure, which improved again when the material was discontinued and interrenalin resumed. At present, he is in excellent condition, has gained in weight, and pigmentation appears decidedly less marked. The following condensed record of the first of these two cases illustrates, strikingly, the beneficial influence of interrenalin in prolonging life and maintaining a fair state of health, in Addison's disease.

*Case S B*, laborer, 42 years of age, was admitted to hospital for hemiotomy July 25, 1933. Six years ago he had had double hemiotomy. Two years ago he was operated for recurrent right hernia. Hemiotomy was performed July 26, 1933. The operation led to development of an acute shock like condition which was distinguishable from surgical shock but not accounted for. On Aug. 2, 1933 consultation (JMR) was requested. Patient reported anorexia and gradual loss of weight during the past 2 years, had an aversion to fat in diet, there was nausea but no vomiting. This was associated with pigmentation appearing first in the skin of the face and becoming uniform over neck, shoulders, arms and hands, and particularly accentuated in areas of normal pigmentation. There are pigment patches on the buccal mucosa, tongue, gums and margin of mucosa of lips. Asthenia, compelled to give up his work for past year. Blood pressure 100/60 mm Hg. BMR +9, blood NPN 41 mg %, urea N 14 mg %, sugar 83 mg %. Another test showed an NPN of 81, urea 15, sugar 86 and NaCl 316 mg %. Rogoff's sign was positive on both sides, but was more marked on right. Diagnosis, Addison's disease. Intravenous administration of saline dextrose solution twice daily for few days, then once daily with oral administration of interrenalin was recommended. Decided improvement followed treatment and on Aug. 13, 1933 the blood pressure was 120/88 mm Hg and the patient was much stronger and up and about. The patient was discharged from the hospital on Aug. 14 and was referred to me for further study and treatment. For more than a year thereafter he required intravenous injections of salt solution at intervals, in addition to oral administration of interrenalin. A number of more or less severe acute exacerbations indicated the need for these injections. Since then he has had no treatment other than interrenalin, except that he favors salty food and fish, and avoids red meats.

In the 8 years that the patient has been under observation, he has maintained a fairly constant weight. The areas of pigmentation in the mucus membrane of mouth and on the tongue are larger than when first observed, and the intensity of color is greater on the exposed parts of the body. Pigmentation at times appears more intense than at other times. This can be related to the general condition, the pigmentation seemingly being intensified when he approaches a subacute state and his circulation is less efficient. As he improves, his color appears lighter. Blood pressure is maintained at an average level of about 110/78 mm Hg. The mental state, which previously was marked by anxiety and worry, has become much less troublesome, he has cooperated admirably, knows the true nature of his ailment, and has repeatedly presented himself, upon re-

quest, for demonstration at medical meetings and class lectures.

The practice of administering salt tablets by mouth does not seem desirable. One of the most aggravating symptoms in Addison's disease is gastric irritability, and excessive amounts of salt frequently cause emesis. It is preferable to include a moderate excess of salt in the regular diet, without additional salt medication. Addisonian patients almost invariably crave salt and take adequate amounts in their food. In acute crisis, or in milder subacute exacerbations, intravenous administration of physiologic salt solutions usually prove strikingly beneficial. The additional liquid in the circulation appears to be the chief beneficial agent, since improvement was observed in adrenalectomized animals, when isotonic dextrose solution, without salt, was administered intravenously. It may be that the increased water intake resulting from oral salt therapy, rather than the salt itself, accounts for much of the improvement that is usually attributed to administration of NaCl in Addison's disease and in experimental adrenal cortical insufficiency.

Often, patients with Addison's disease in an apparently moribund state, like adrenalectomized animals, may be resuscitated from coma by intravenous administration of physiological liquids. The recovery sometimes is quite spectacular, occurring during the injection and before physiologic effects of NaCl would be expected. This can explain some of the striking results that have been reported from the use of certain extracts, especially those of doubtful merit or of admitted impotency, when administered intravenously together with saline solutions. The remarkable symptomatic improvement which results from intravenous administration of fluid, and the potential possibility of spontaneous remission in the course of this disease, sometimes may be misleading when evaluating the effect of substitution therapy.

The therapeutic effect of adrenal cortex extract can not be expected to result as rapidly as, for example, that of epinephrin with its production of hemodynamic effects or insulin with its effects on glycemia. Metabolic effects of thyroid medication are perhaps more comparable. Correction of the severe, complex metabolic disturbances in Addison's disease requires much longer for the physiologic readjustments that must be effected. The very nature of this disease, its etiology and pathology indicate the improbability of a rapid physiologic readjustment.

As a routine procedure in the treatment of Addison's disease, interrenalin is administered in the form of a potent adrenal cortex extract, which has proven to be effective by mouth. At suitable intervals, this has been supplemented by intravenous injections of saline dextrose solution. Parenteral administration of



interrenalin is useful at times when gastric irritability interferes with oral administration. At such times intravenous saline is essential, and sterile adrenal cortex extract can be included. However, it appears that exacerbations may be prevented, or their frequency and severity minimized, by an occasional series of routine intravenous injections of saline-dextrose solution. This should be done at once if it is observed that the N.P.N. in the blood is increasing.

In all of the observations on treatment of Addison's disease since 1925, the interrenalin employed clinically, by mouth, has been prepared in glycerinated solution, the extract first having been properly tested for potency by its capacity to prolong life in completely adrenalectomized male dogs well beyond the maximum period of survival of untreated control animals. One assay method that has been suggested (9) is based on the capacity of an extract to prevent a rise in N.P.N. or in urea N for a period of 7 to 10 days, in adrenalectomized dogs. Since this is the period of good health in untreated adrenalectomized dogs, when the N usually does not yet increase significantly, the method can not be considered useful.

Potent extracts can be obtained by various modifications of the original process developed between 1917 and 1922, activity of products being demonstrated in 1925 (1). This consists of extraction of adrenal cortex with alcohol or acetone, and purifying by subsequent action of selective solvents, leaving the active interrenalin in aqueous solution. This solution can be concentrated and glycerinated for oral administration, or it can be prepared as a sterile solution for parenteral administration. Combined in tablet form, interrenalin has recently been made available commercially<sup>4</sup> for oral administration. Extraction of these tablets and tests of the extract for potency has demonstrated that the product is capable of prolonging life in adrenalectomized male dogs.

Aside from the therapy already discussed, it is advisable to restrict muscular exertion to exercise sufficient to meet physiologic requirements. Muscular fatigue and nervous tension should be avoided since they often precipitate an exacerbation. Adequate attention to eliminative functions is, of course, necessary. It is well to regulate the diet, limiting the protein intake to minimum requirements and favoring carbohydrate. As already stated, patients crave and take a surplus of salt. If they do not, this should be encouraged. It has not been found necessary to be much concerned about ordinary potassium intake. The amount of potassium in the usual diet of a patient with Addison's disease is not significant. Certainly, if an excess of K, or of any other toxic substance, is part of the diet it can be injurious. The

saltpetre in pickled meats, for example, has caused subacute manifestations in one case under my observation.

*Synthetic drugs.* Desoxycorticosterone acetate, a synthetic drug represented as a product corresponding to the adrenal cortical hormone, has been alleged to produce benefit in the treatment of Addison's disease (10). Administration by subcutaneous implantation of pellets has attracted some attention. It is assumed that this permits slow, gradual, quantitative absorption of the drug, thus avoiding the need for more frequent injections of soluble material. The evidence for this does not appear convincing from a pharmacologic viewpoint. It does not seem a good substitute for quantitative administration when a soluble preparation is available, even if use of the drug were desirable and safe.

Recent reports (11) on the use of this material in Addison's disease indicate that the enthusiasm which marked earlier publications was somewhat premature. The duration of treatment, in cases alleged to have been benefited by the drug, was too short to permit proper evaluation. Supposed benefit in some cases may be explained by the fact that salt, adrenal cortex extract, or both, were also administered during the period of treatment. Furthermore, it will be more convincing if a number of the cases treated with this material will show definite prolongation of life. Confirmation of the diagnosis at autopsy may seem desirable in some cases.

Desoxycorticosterone acetate appears to be not only less, if at all effective in Addison's disease, than potent extract of adrenal cortex, but it has been demonstrated to possess extremely dangerous, toxic properties. The statement (12), that "The treatment of Addison's disease with desoxycorticosterone acetate represents a marked advance in therapy," is associated with striking evidence which proves the very antithesis to that statement. Five cases of Addison's disease were reported. Treatment with desoxycorticosterone acetate was followed in all of them by serious toxic manifestations; among these were pathologic hypertension, cardiac embarrassment and marked edema. In 3 of the cases, actual cardiac failure was caused. The periods of observation under this treatment ranged from 1 to 6 months. Whatever improvement was observed in some of the patients could be attributed to the influence of salt, which all of the patients received or, in some of the cases, to the adrenal cortex extract that was also employed; and it may have been due to the spontaneous improvement that characterizes Addison's disease. While gain in weight is an encouraging clinical observation, this usually favorable circumstance might sometimes be viewed with alarm by the physiologist. In one of

<sup>4</sup> Cortalex, Upjohn Company, Kalamazoo, Michigan.

the cases, the patient showed a gain of 12 pounds in 4 days. This observation, in the light of existing cardiac embarrassment and edema, may be interpreted as an indication of pathologic retention of water, which is reflected in a gain of weight. It appears that the action of desoxycorticosterone acetate does not represent the physiologic rôle of interrenalin, neither is it a satisfactory substitute for properly tested adrenal cortex extract. Its use in Addison's disease can be considered dangerous because of its serious toxic properties (11).

#### COMMENT

From the foregoing discussion on treatment, there can be little or no doubt about the therapeutic value of properly tested, potent adrenal cortex extract in Addison's disease. Reports in the literature appear confusing as the result of too brief periods of observation, and inadequate criteria for effectiveness of treatment.

As in adrenalectomized animals, the only reliable criterion for determining the efficacy of treatment in Addison's disease is definite prolongation of life. Prior to the introduction of treatment with interrenalin, with or without supplementary administration of salt, the maximum duration of the disease was about  $1\frac{1}{2}$  to 2 years. This is revealed from the history of cases, proven at autopsy, and recorded by responsible observers (13). Twelve cases that were observed before the present treatment was developed survived for about the same periods as reported by these authors (4).

Accordingly, evaluation of results of treatment with adrenal extracts, synthetic drugs, or other therapy in Addison's disease of less than 2 years in duration, may be misleading. At most, the results could testify to mitigation of symptoms. In this respect, it should be emphasized that spontaneous remission, sometimes surprisingly abrupt, is a characteristic of Addison's disease. Such a remission might be attributed, mistakenly, to whatever treatment is employed at the time.

Usually, the diagnosis of Addison's disease presents no great difficulty, yet it can not always be made with certainty. There is no one constant, specific or pathognomonic sign by which accurate diagnosis can be assured. At present, absolute certainty of the diagnosis can be established only postmortem. Therefore, to evaluate the potency of adrenal cortex extract, by clinical test in Addison's disease, convincing evidence can be obtained only from those cases that ultimately have come to autopsy. Controversial questions can thus be entirely avoided. The criterion must be as unambiguous as in the case of adrenalectomized animals, and therefore the same, i.e., definite

prolongation of life. For convincing evidence, cases treated with adrenal cortex extract should be compared with similar cases not so treated, and total duration of survival determined in both groups.

A previous report (4) included 21 cases of Addison's disease that were treated with interrenalin, and 12 cases that did not receive this treatment. One patient, case 17, left the city after a year of treatment, markedly improved, and we have been unable to locate him. Six of the remaining patients were still living at the time of publication. Control of two, (cases 10, 18) was lost in 1934. Two patients died since the report was published, having survived  $1\frac{1}{2}$  and more than  $3\frac{1}{2}$  years, respectively, from the time of onset of definite symptoms. In the first of these 2 cases, autopsy revealed bilateral extensive caseous degeneration of the adrenals, tuberculosis of the lungs and the right knee joint, and miliary tubercles in the liver and kidneys. The other patient had clinical evidence of tuberculosis, but an autopsy was not obtained.

In the cases treated with interrenalin, the duration of survival from the period of onset of the related symptoms ranged between 1 and  $7\frac{1}{2}$  years. Diagnosis of Addison's disease was confirmed at autopsy in 10 cases of this group. Of the 12 cases that were not treated with interrenalin the diagnosis was confirmed at autopsy in 7. Total duration of the disease in this group ranged between  $\frac{1}{2}$  and  $1\frac{1}{2}$  years. Four of the 7 cases had bilateral extensive adrenal atrophy, two caseous and one hyaline degeneration. In the other group, four presented marked atrophy, one extensive atrophy and fibrosis of the left adrenal and practically complete calcification of the remains of the right gland, one granulomatous degeneration, one malignant neoplasm, two caseous degeneration, and one caseous degeneration with calcification.

The number of cases is not large enough to subject to mathematical treatment. However, comparison of the duration of survival of the patients in the treated with the untreated group reveals the longer survival of the interrenalin treated patients. The average survival period for the treated cases was about 4 times as long as for the cases in the untreated group. Of the 20 patients receiving interrenalin, 8 survived between 1 and 2 years while 12 survived between  $2\frac{1}{2}$  and  $7\frac{1}{2}$  years.

Limiting the comparison to the cases in which the diagnosis of Addison's disease was confirmed at autopsy, the average duration of survival in the cases that were treated with interrenalin was approximately 3 years (maximum  $5\frac{1}{2}$ ). The average in the group that were treated otherwise was about 0.8 of a year (maximum  $1\frac{1}{2}$ ). The fact that in a significant proportion of the interrenalin treated cases length of

survival greatly exceeded the maximum survival period of the non-treated cases, is, of course, much more important even than the facts revealed by comparison of averages.

These data constitute a clear and unmistakable demonstration of the beneficial influence of interrenalin, in the treatment of Addison's disease. Mitigation of severity of one or more symptoms alone is not enough to prove effectiveness of treatment. Only decided prolongation of life is a reliable criterion for determining the real value of specific substitution therapy in Addison's disease. The potency of an adrenal cortex extract that is administered should be determined by its capacity to prolong life and good health well beyond the maximum period of survival of suitable control animals, in completely adrenalectomized male dogs.

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# Effect of Adrenal Cortical Extract, Desoxycorticosterone, and Added Potassium upon Electrolyte Balance in Normals and in Addison's Disease

## [Electrolyte Balance]

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THE DIAGNOSTIC METHODS for adrenal cortical insufficiency are not entirely satisfactory. A reliable one is not available for the diagnosis of mild insufficiencies and those for Addison's disease are not without hazard. The production of a crisis by a high potassium intake either alone or in combination with a low sodium intake is dangerous.

The Wilder (1) method in which a high potassium and low sodium intake are administered for a shorter period is the safest procedure, yet crises continue to develop with this test. It was pointed out in a previous report (2) that patients with Addison's disease are more sensitive to added potassium during periods of sodium chloride depletion than following correction of this depletion. It was also emphasized that sodium chloride restriction can be tolerated for long periods provided the sodium chloride stores are not depleted and provided that the potassium intake is low. Such restriction, however, with the sodium chloride stores depleted may provoke a crisis. These hazards have caused us to consider other possible diagnostic methods.

In a previous study (2) it was noted that adrenal cortical extract did not cause patients with Addison's disease to store sodium at a faster rate provided the sodium intake was high and the potassium intake was low. Hartman (3) and his coworkers, on the other hand, have reported that adrenal cortical extract caused a retention of sodium in normal men. This apparent difference in the reaction of normal men and of patients with Addison's disease to the administration of adrenal cortical extract appeared as a possible diagnostic method which would be free of hazards. The present study was undertaken, therefore, to

ascertain the response under identical circumstances of normal persons and of patients with Addison's disease to the administration of a) adrenal cortical extract, b) of desoxycorticosterone, c) of extra potassium, d) of adrenal cortical extract administered simultaneously with extra potassium, and e) whether or not any differences in response could be of diagnostic value in Addison's disease.

### METHOD

Balance studies were made on sodium, chloride, and potassium in 3 normal subjects and in 3 patients with Addison's disease. All subjects received a Na intake of 12 gm and a K intake of 2 gm daily except when extra K was added. The study was made in 3 day periods, a control period usually preceded each experimental period and as a rule, 3 to 5 days elapsed between each series of study. The adrenal cortical extract was administered intravenously on the morning of the first day of the 3-day period in doses from 1,500 to 2,500 dog units, desoxycorticosterone acetate in oil was administered intramuscularly the first morning in 25 mg doses. The potassium citrate was administered orally in amounts equivalent to 6 gm of K daily for the period of added potassium intake and also for the period of simultaneous administration of extra potassium and the adrenal cortical extract. The extract was administered intramuscularly daily during this period in doses of from 250 to 750 dog units. In 3 instances a recovery period followed the period of added potassium and extract administration. The daily urinary creatinine and nitrogen were measured in each instance and blood Na and serum K were measured during each period. The methods for analysis were the same as in the previous report (2).

TABLE 1. EFFECT OF ADRENAL CORTICAL EXTRACT ON SODIUM, POTASSIUM AND CHLORIDE BALANCE

| Patient No.              | Period   | Average Daily Sodium Balance gm. | Average Daily Chloride Balance gm. | Average Daily Potassium Balance gm. |
|--------------------------|--|----------------------------------|------------------------------------|-------------------------------------|
| <i>Addison's disease</i> |  |                                  |                                    |                                     |
| 1                        | Control  | +5.09                            | +4.59                              | +0.57                               |
|                          | After 1500 dog units of adrenal cortical extract | +4.91                            | +4.58                              | +0.72                               |
| 2                        | Control  | +2.51                            | +1.55                              | +0.28                               |
|                          | After 2500 dog units of adrenal cortical extract | +2.33                            | +0.81                              | +0.37                               |
| 3                        | Control  | +1.39                            | +1.16                              | +0.26                               |
|                          | After 2500 dog units of adrenal cortical extract | -0.13                            | -0.71                              | -0.22                               |
|                          | Control  | +0.05                            | -0.33                              | -0.27                               |
|                          | After 25 mg. desoxycorticosterone                | +1.64                            | +0.91                              | -0.72                               |
| <i>Normal subjects</i>   |  |                                  |                                    |                                     |
| 1                        | Control  | +0.06                            | -1.10                              | +0.16                               |
|                          | After 2500 dog units of adrenal cortical extract | +1.57                            | +1.07                              | +0.37                               |
| 2                        | Control  | -0.85                            | -0.82                              | -0.03                               |
|                          | After 2500 dog units of adrenal cortical extract | +1.01                            | +1.54                              | -0.03                               |
| 3                        | Control  | +0.51                            | -0.34                              | +0.34                               |
|                          | After 25 mg. desoxycorticosterone                | +1.58                            | +1.05                              | +0.11                               |

## RESULTS

*Effect of adrenal cortical extract and of desoxycorticosterone.* It is to be noted from table 1 that the patients with Addison's disease did not store any more sodium

TABLE 2. EFFECT OF ADDED POTASSIUM ON SODIUM, POTASSIUM AND CHLORIDE BALANCE

| Patient No.              | Period        | Average Daily Sodium Balance gm. | Average Daily Chloride Balance gm. | Average Daily Potassium Balance gm. |
|--------------------------|---------------|----------------------------------|------------------------------------|-------------------------------------|
| <i>Addison's disease</i> |               |                                  |                                    |                                     |
| 1                        | Control       | +4.09                            | +3.27                              | -0.41                               |
|                          | 6 gm. added K | +4.14                            | +4.00                              | +3.80                               |
| 2                        | Control       | +0.18                            | -1.45                              | +0.22                               |
|                          | 6 gm. added K | -0.76                            | -2.62                              | +3.83                               |
| 3                        | Control       | +0.71                            | -0.04                              | -0.20                               |
|                          | 6 gm. added K | -1.57                            | -2.61                              | +4.32                               |
| <i>Normal subjects</i>   |               |                                  |                                    |                                     |
| 1                        | Control       | +0.91                            | +0.30                              | +0.26                               |
|                          | 6 gm. added K | -0.51                            | -1.09                              | +1.64                               |
| 2                        | Control       | +0.43                            | +1.15                              | +0.03                               |
|                          | 6 gm. added K | -1.10                            | -0.53                              | +1.71                               |

following the administration of adrenal cortical extract during periods of high NaCl and low K intake. The normal subjects, on the other hand, did show a retention of sodium even with a high Na intake and there was no apparent initial sodium depletion. A retention of sodium, however, by both the patients and normal subjects was observed following the administration of desoxycorticosterone even though the Na intake was high and there was no Na depletion. The chloride balances followed closely those of sodium and there were no consistent alterations of the K balances. These observations confirm our previous findings that the administration of adrenal cortical ex-

TABLE 3. EFFECT OF POTASSIUM AND ADRENAL CORTICAL EXTRACT ON SODIUM, POTASSIUM AND CHLORIDE BALANCE

| Patient No.              | Period   | Average Daily Sodium Balance gm. | Average Daily Chloride Balance gm. | Average Daily Potassium Balance gm. |
|--------------------------|--|----------------------------------|------------------------------------|-------------------------------------|
| <i>Addison's disease</i> |  |                                  |                                    |                                     |
| 2                        | Control  | +0.18                            | -1.45                              | +0.22                               |
|                          | 6 gm. added K  | -0.76                            | -2.62                              | +3.83                               |
|                          | 6 gm. added K plus 250 dog units of adrenal cortical extract daily | -1.17                            | -4.07                              | +1.83                               |
|                          | 6 gm. added K plus 750 dog units of adrenal cortical extract daily | -1.76                            | -9.48                              | -4.72                               |
| 3                        | Control  | +2.44                            | +0.29                              | -2.16                               |
|                          | 6 gm. added K plus 750 dog units of adrenal cortical extract daily | +1.97                            | +2.18                              | -1.03                               |
|                          | Control  | +1.20                            | +0.68                              | +4.98                               |
|                          | Control  | +1.30                            | +1.35                              | -1.38                               |
| <i>Normal subjects</i>   |  |                                  |                                    |                                     |
| 1                        | Control  | +0.91                            | +1.65                              | -0.18                               |
|                          | 6 gm. added K plus 750 dog units of adrenal cortical extract daily | +0.46                            | -0.55                              | +2.18                               |
|                          | Control  | +2.05                            | +1.75                              | -0.24                               |

tract to patients with Addison's disease does not cause an acceleration of Na storage and they confirm the work of Hartman and coworkers (3) that the extract causes a retention of sodium in normal subjects. Desoxycorticosterone, on the other hand, causes a retention of Na in normal subjects and in the patients.

*Effect of added potassium.* The effect of the administration of potassium to the patients and the normal subjects is shown in table 2. It should be emphasized that there was no Na depletion in patients 2 and 3, whereas, patient 1 was still storing sodium. With the addition of potassium the patients stored less Na when the sodium stores were saturated, but it had no effect when the Na stores were partially depleted. The addition of K also caused the normal subjects to

store less sodium. The chloride metabolism coincided with that of sodium. The patients stored more of the added K than did the normal subjects, and a crisis developed in the first 2 patients, but not in the third.

**Effect of added potassium and adrenal cortical extract.** The above observations that the normal subject stored less of the added potassium than did the patients indicated that the simultaneous administration of adrenal cortical extract may decrease the storage of K by the patients. It is to be noted from table 3 that such an effect was apparent in patient 2, whereas patient 3 stored just as much K as in the period without the extract (table 2). It should be noted, however, that patient 2 received extra K for 9 successive days. During the first 6 days approximately 17.0 g. of K were stored and during the next 3 days approximately 14.0 gm. were excreted. It is of interest that the patient developed manifestations of mild crisis, namely, weakness, hypotension, abdominal cramps, and diarrhea during the last 3 days when he was in negative K balance. It is possible that the administration of the adrenal cortical extract prevented a more severe crisis and caused the excretion of the potassium. The fact that patient 3 stored just as much K with or without the extract casts some doubt upon this explanation. The data are insufficient to draw any conclusions. The administration of adrenal cortical extract apparently lessened, but did not prevent a decrease in Na retention with the addition of potassium. There was apparently no difference in the response to the addition of adrenal cortical extract and the extra K in the normal subject (comparison of tables 2 and 3).

#### COMMENTS

The response of normal subjects to adrenal cortical extract and desoxycortisterone differs in several respects from that of patients with Addison's disease and the differences may be of diagnostic value. The continued high urinary excretion of sodium chloride during restricted intake is one difference and is well known; it is the basis for the diagnostic method advocated by Wilder and his associates (1). This procedure may be hazardous if the patient's sodium stores are greatly depleted. Our previous study suggests that if this diagnostic procedure is to be employed the hazard of crisis developing may be greatly reduced by correcting to a large extent the existing sodium depletion by a high sodium and low potassium intake for several days prior to the test. The greater urinary excretion of sodium chloride by normal subjects than by patients during a high sodium chloride and low potassium intake as shown in this study may be of diagnostic value. Its value would depend upon a state of Na depletion in the patient with Addison's disease and upon the assumption that the suspected patient did

not have sodium depletion. Such a procedure would be relatively free of serious hazards, but depletion of the sodium stores would undoubtedly be encountered in many patients without Addison's disease. Thus the method probably would not be of specific diagnostic significance.

The second difference is the response to added potassium. It has been emphasized by Wilder and his associates (4) that the addition of potassium will provoke a crisis in patients with Addison's disease; they observed a greater urinary excretion of sodium chloride. An induction of a crisis by additional potassium intake has been confirmed (2). It was pointed out in our previous report that patients with Addison's disease were more sensitive to potassium if the sodium stores were greatly depleted than if they were nearer normal. Such a response depends, therefore, upon the sodium stores of the patient. Patients with slight sodium depletion would require larger amounts of potassium, whereas, in patients whose sodium stores were depleted such a dose of potassium would quickly provoke a severe and possibly fatal crisis. The induction of crisis by added potassium entails too great a risk for a routine diagnostic procedure. The greater urinary excretion of sodium chloride by patients following the administration of extra potassium has not been uniform in our studies, normal subjects will also excrete a greater amount of sodium chloride. Patients with Addison's disease will excrete less of the extra potassium than will normal subjects as shown in table 2. This difference in response, however, entails the possibility of provoking a crisis and should not be considered as a diagnostic method.

The third difference between normal subjects and patients is in their response to the administration of adrenal cortical extract and a high sodium and low potassium intake. Our present study indicates a definite difference in the response of patients with Addison's disease to that of normal subjects. If this difference is subsequently confirmed it should be an excellent diagnostic method. There should not be any chance to provoke a crisis. The outstanding difficulty would be the cost of administration of large amounts of adrenal cortical extract. The response apparently depends upon a high sodium chloride intake and possibly a low potassium intake. The cause for this difference in response is not known. Hartman and coworkers (5) have been able to separate the sodium retention factor from the life preserving factor of adrenal cortical extract. It appears, therefore, that the extract employed by us did not contain much of the sodium retention factor, but that there was a sufficient amount of it to cause a sodium retention, provided the adrenal glands of the subject were also secreting some of this factor. That desoxycorticosterone acetate contains more of the sodium retention

factor is shown by the retention of sodium by the patients and by the normal subjects. The response to administration of desoxycorticosterone acetate would not be of diagnostic value.

Adrenal cortical extract will cause a greater retention of sodium in patients with Addison's disease if the patient has a low sodium and potassium intake as shown in our previous study (2). We have been unable to find comparable studies on normal subjects. The fact that normal individuals will store more sodium with a high sodium chloride intake makes it appear likely that they will also store sodium with a low intake. If this be true this response would not be of diagnostic value. There is not a sufficient difference between the response of normal subjects and of patients with Addison's disease to the simultaneous administration of extra potassium and adrenal cortical extract to be of diagnostic significance. The greater retention of potassium during these periods by the patients than by normal individuals may be significant, but the possibility of induction of a crisis would limit its applicability.

#### SUMMARY

Normal subjects and patients with Addison's disease have been studied under conditions of high so-

dium chloride and low potassium intake as a basis for deriving possible diagnostic methods. The response to administration of adrenal cortical extract, desoxycorticosterone acetate, extra potassium, and to simultaneously administered extra potassium and adrenal cortical extract has been ascertained. The various possible diagnostic methods are discussed and it has been suggested that the difference in response of normal subjects to administration of adrenal cortical extract from that of patients with Addison's disease may be the basis of a safe and specific test.

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# Preoperative Administration of Desoxycorticosterone Acetate in the Prevention of Surgical Shock<sup>1,2</sup>

## [Prevention of Surgical Shock]

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PERLA AND HIS ASSOCIATES (1) recently reported that administration of desoxycorticosterone acetate would protect experimental animals from histamine shock. They found that previous administration of solutions of sodium chloride and desoxycorticosterone acetate was more effective than the use of the latter alone. They further administered sodium chloride and desoxycorticosterone acetate preoperatively to patients who were to undergo major surgical procedures. Using as criteria the clinical condition of the patient and the impression of the attending surgeon they felt that they had demonstrated that such preoperative treatment effectively prevented the occurrence of postoperative shock.

On the basis of these observations Perla and his associates advocated the preoperative administration of desoxycorticosterone acetate in all instances in which surgical shock might be anticipated. Widespread trial of this suggestion apparently has been made, but no convincing confirmation has been forthcoming. Because of the possible importance of any such effect, both in war medicine and in general surgery, it was felt desirable to investigate the problem critically and objectively in human subjects.

Any rationale for the use of adrenal cortical extracts or adrenal cortical steroids (such as synthetic desoxycorticosterone acetate) in the prevention or in the treatment of states of shock must accept at least in part the hypothesis of Selye and his associates (2) that such states are associated with a relatively acute adrenal cortical insufficiency resulting from a sudden unfulfilled need on the part of the tissues for the secretion of the adrenal cortex. Acute adrenal cortical insufficiency has been studied intensively as it occurs in human subjects in the crisis of Addison's disease

and in adrenalectomized animals. Characteristic and profound changes in the composition of both the blood and the urine occur in acute adrenal cortical insufficiency and these changes, with the possible exception of hypoglycemia, are counteracted rather rapidly by the administration of desoxycorticosterone acetate. It appeared profitable to look for similar changes in the blood and urine of patients suffering from surgical shock or in patients who had undergone major surgical procedures in the absence of shock, and, if they occurred, to determine whether preoperative treatment with desoxycorticosterone acetate might prevent or abolish them.

The results of observations on 19 women undergoing radical mastectomy for treatment of carcinoma of the breast form the material for this study. This operation was selected for a number of reasons: a), It is an extensive surgical procedure which frequently is associated with surgical shock by reason of the extent of the operative trauma, the length of the operation, the fairly extensive loss of blood which occurs, and the deep anesthesia required; b), Patients could be selected who were in good health except for the presence of a mass in the breast and who therefore could be regarded as otherwise essentially normal subjects; c), Ether is usually the anesthetic of choice at the Mayo Clinic in this procedure. It was felt that for the present study ether was preferable to any other anesthetic agent because its effect on the volume and composition of the blood is such as to favor the production of shock and because ether has been the object of more study than have other anesthetic agents; d), The operation is one in which for purposes of study the preoperative and postoperative management can be standardized fairly well; e), The abdominal cavity is not involved in the operation, consequently many troublesome and uncontrollable factors affecting metabolism of fluids and electrolytes are avoided.

We are deeply indebted to the members of the Division of Surgery and the Section on Anesthesia

<sup>1</sup> Read before the twenty-fifth annual meeting of the Association for the Study of Internal Secretions, Atlantic City, New Jersey, May 2, 1931.

<sup>2</sup> *Abstracts*, p. 7.

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for their many suggestions and wholehearted coöperation, without which the study would not have been possible.

#### METHODS

Ten of the patients in this series were not given any desoxycorticosterone acetate and served as controls. The remaining 9 were given the hormone preoperatively as described later. Both the control and the treated groups were studied in the following manner. Blood for analysis was drawn immediately before the operation; in most cases a specimen was obtained during the evening preceding the operation. Subsequent specimens were obtained during the operation prior to any intravenous medication (if such was given), at the end of the operation, and 1.5 hours, 24 hours and in some cases 48 hours after operation. The samples of blood were drawn into a syringe containing heparin and oil, stirred by means of a glass bead in the syringe, immediately transferred under oil to an hematocrit tube, transported in ice and at once centrifuged in a cold centrifuge (20° F.) at 2,800 r.p.m. for 15 minutes. The plasma then was removed and the remainder centrifuged for a total of 2 hours to complete the hematocrit determination.

The plasma was examined for its specific gravity by a falling drop method, and for its content of chloride, potassium and nitrogen. Nonprotein nitrogen and total nitrogen also were determined and from these figures the total plasma protein was calculated. The methods of analysis employed are referred to elsewhere (3).

All urine passed during the remainder of the operative day was collected, as was the 24-hour specimen for the following day. This was analyzed for its content of chloride and sodium. Careful clinical notes were kept of the patient's course during and after operation. The blood pressure was recorded at intervals of 5 minutes during the operation and hourly (or more frequently when necessary) for 24 hours. An effort was made to form an estimate of the volume of blood lost during the operation by grading it on a basis of 1 to 4. The average blood loss was graded 3, excessive quantities 4 and lesser amounts 1 or 2. Careful record was kept of the time relations between the taking of the blood samples, the duration of administration and the amount of the anesthetic agent, the duration of the operation, the character and amount of intravenous fluids administered, and so forth.

#### RESULTS

Desoxycorticosterone acetate in sesame oil was administered subcutaneously in a single site. One patient was treated with a modification of the regimen proposed by Perla and associates. The patient was hospitalized for 4 days before the operation and each

day she received desoxycorticosterone acetate subcutaneously. On the first 2 days she received 10 gm. of NaCl by mouth. On each of the 2 days preceding the operation she received an intravenous injection of 1,500 cc. of physiologic solution of NaCl; extra salt was not given by mouth. The entire preoperative treatment period was conducted as a 'balance study' to determine as precisely as possible what effect was produced by this method. All food was weighed and its salt content calculated; the water intake was kept high and measured accurately. All urine was analyzed for its content of Cl, Na and K. The patient was weighed accurately each day. Significant retention of both salt and water took place, particularly on the day preceding the operation. The patient withstood *operation extremely poorly; she bled profusely, exhibited the typical signs of operative shock and presented a most difficult problem for the anesthetist because of an excessive amount of moisture in the lungs.* An underlying cardiac condition was suspected as the cause of some of these difficulties, but the effect of the excessive hydration produced by means of the preoperative treatment could not be ruled out as a factor.

It was thought preferable to see if desoxycorticosterone acetate alone, without the factor of preoperative hydration, would produce changes which might appear of value in preventing shock. Two patients were studied by the subcutaneous administration of 20 mg. of desoxycorticosterone acetate 6 hours prior to operation, no other change being made in the routine preoperative care. This period was selected because in experimental studies it had appeared to be an adequate period for the appearance of the effects of desoxycorticosterone acetate.

When the results of treatment of these two patients were unequivocally negative, it was felt that larger doses might be required. The remaining 6 patients were given 40 mg. of desoxycorticosterone acetate in two doses of 20 mg. each. The first dose was given at 9 P.M. of the day before the operation (12 to 14 hours before operation) to ensure that the maximal effect of the hormone would be present during the operation and a second dose was given 2 to 3 hours before operation to ensure a prolonged effect after operation.

Since the results of all three methods described appeared identical, they are summarized in the tables without particular regard for the dose or the method of administration.

#### COMMENT

In tables 1 and 2 are summarized some of the clinical data on the two series of patients. The patients in the treated series had an average age of 52.7 years; those in the control series an average age of 50.2 years.

The duration of the operation in the treated group averaged 77 minutes, in the control group 80 minutes. Fortunately the quality and quantity of intravenous fluids administered in the two groups were also comparable. However, sufficient variation was present in the total intake and urinary excretion of fluids to limit seriously the value of the data obtained from the analysis of the urine.

Genuine shock with all its concomitants cannot be said to have been encountered in any instance in either group. No evidence of hemoconcentration was found, all the shocklike states which occurred were relatively mild and responded to treatment. No fatalities occurred and without exception the patients made reasonably rapid recovery after the operation. This is not surprising when it is considered that in the modern hospital the earliest appearance of any of the signs of shock is the signal for prompt and vigorous treatment. The patients comprising this study were treated exactly as they would have been had no study been in progress.

However, a number of patients exhibited states to which the term 'shock' usually is applied, perhaps 'incipient' or 'early' shock would be more accurate terms. Profound fall of blood pressure, a weak, thready pulse, pallor and sweating were encountered frequently during the operation, usually about the time of the removal of the breast or shortly thereafter. Such symptoms were the indication for the intrave-

good pulse and normal blood pressure the patient on return to her bed would present the clinical picture of collapse, including slow respiration, feeble pulse, sweating, pallor and a fall in blood pressure, and would be extremely slow in recovering from the effects of the anesthetic. In these cases the patient responded in from 6 to 8 hours with no other treatment.

TABLE 2 TREATED PATIENTS

| Case | Age of Patient, yr | Treatment      |             | Duration of Operation, min | Amount of Bleeding, grade <sup>1</sup> | Shock Symptoms   |                 |
|------|--------------------|----------------|-------------|----------------------------|--|------------------|-----------------|
|      |                    | Total dose, mg | No of doses |                            |  | During operation | After operation |
| 11   | 41                 | 20             | 1           | 68                         | 3                                      | +                | +               |
| 12   | 65                 | 20             | 1           | 92                         | 3                                      | +                | 0               |
| 13   | 69                 | 50             | 5           | 95                         | 3                                      | +                | 0               |
| 14   | 57                 | 40             | 2           | 85                         | 3                                      | +                | +               |
| 15   | 68                 | 40             | 2           | 80                         | 1                                      | +                | 0               |
| 16   | 38                 | 40             | 2           | 55                         | 3                                      | 0                | 0               |
| 17   | 39                 | 40             | 2           | 55                         | 2                                      | 0                | 0               |
| 18   | 42                 | 40             | 2           | 93                         | 3                                      | +                | 0               |
| 19   | 55                 | 40             | 2           | 68                         | 2                                      | 0                | 0               |

<sup>1</sup> Graded on the basis of 1 to 4, 1 indicates minimal, and 4 maximal, bleeding.

than warmth, Trendelenburg position, and the intravenous administration of fluids. Such postoperative shock was encountered in 2 of the 10 control cases and in 2 of the 9 cases in which desoxycorticosterone acetate had been given. In only one instance (case 4) was much difficulty encountered in improving the state of the circulation.

Four of the patients serving as controls and 3 of those treated with desoxycorticosterone acetate did not exhibit either the signs or the symptoms of shock at any time during or after the operation.

Determinations of the hematocrit value (fig 1), specific gravity of the plasma and total plasma protein (fig 2) were employed as indexes of hemoconcentration. Significant increase in the concentration of the blood was not encountered in either group of patients irrespective of the condition of the patient. Instead, among all patients, treated and controls alike, there was a progressive fall in the values mentioned during and after the operation but no significant differences could be seen between the two series.

The most remarkable feature of the chemical analyses of blood plasma in these cases was the relative absence of any conspicuous variations. Concentrations of plasma electrolytes never varied in either direction beyond the normal range. Differences were far greater between different patients before operation than any variations which occurred in any individual patient after operation. In the control series the concentrations of chloride (fig 3) and sodium (fig 4)

TABLE 1 UNTREATED PATIENTS

| Case | Age of Patient, years | Duration of Operation, minutes | Amount of Bleeding, grade <sup>1</sup> | Shock Symptoms   |                 |
|------|-----------------------|--------------------------------|--|------------------|-----------------|
|      |                       |                                |  | During operation | After operation |
| 1    | 50                    | 65                             | 2                                      | 0                | 0               |
| 2    | 56                    | 45                             | 2                                      | 0                | 0               |
| 3    | 44                    | 60                             | 3                                      | 0                | 0               |
| 4    | 43                    | 100                            | 2                                      | +                | +               |
| 5    | 44                    | 55                             | 3                                      | 0                | 0               |
| 6    | 62                    | 90                             | 3                                      | +                | 0               |
| 7    | 47                    | 110                            | 3                                      | +                | 0               |
| 8    | 65                    | 90                             | 3                                      | +                | +               |
| 9    | 60                    | 90                             | 1                                      | +                | 0               |
| 10   | 31                    | 95                             | 3                                      | +                | 0               |

<sup>1</sup> Graded on the basis of 1 to 4, 1 indicates minimal, and 4 maximal, bleeding.

nous administration of fluids. This state of operative shock occurred in 6 cases in each series. Treatment consisted in the intravenous injection of physiologic solution of NaCl alone in 7 cases, of physiologic solution of NaCl and blood transfusion in 3 cases and of solution of NaCl and acacia in 2 cases.

A second state which might be called 'threshold' or 'abortive' shock occurred postoperatively in a few instances, after leaving the operating room with a

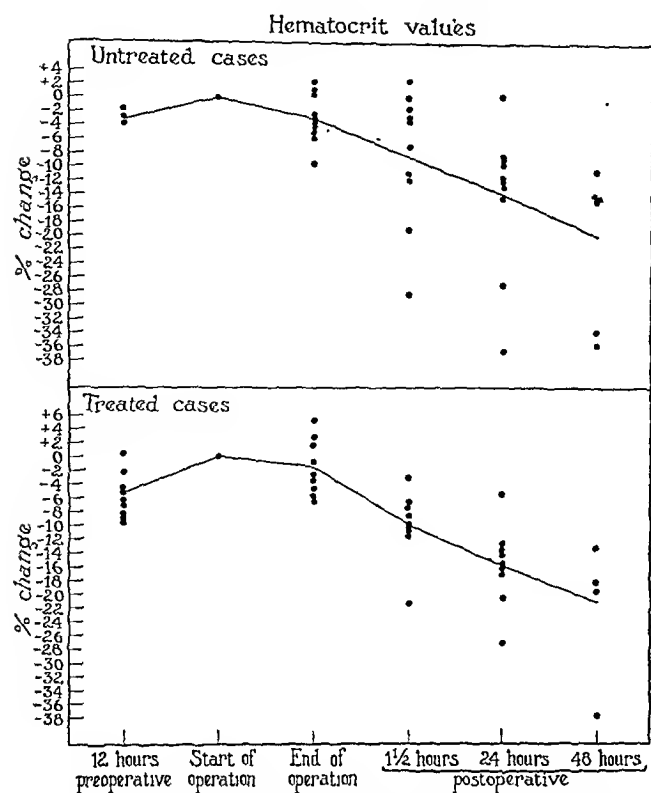


Fig. 1. CHANGES IN HEMATOCRIT VALUES. In this and succeeding figures each determination is expressed as the percentage change from the value of the control specimen obtained immediately preceding induction of anesthesia ('start of operation'). The points representing the average of the values at each interval are connected by the continuous line.

There were no significant differences in the changes of hematocrit in the treated and untreated groups.

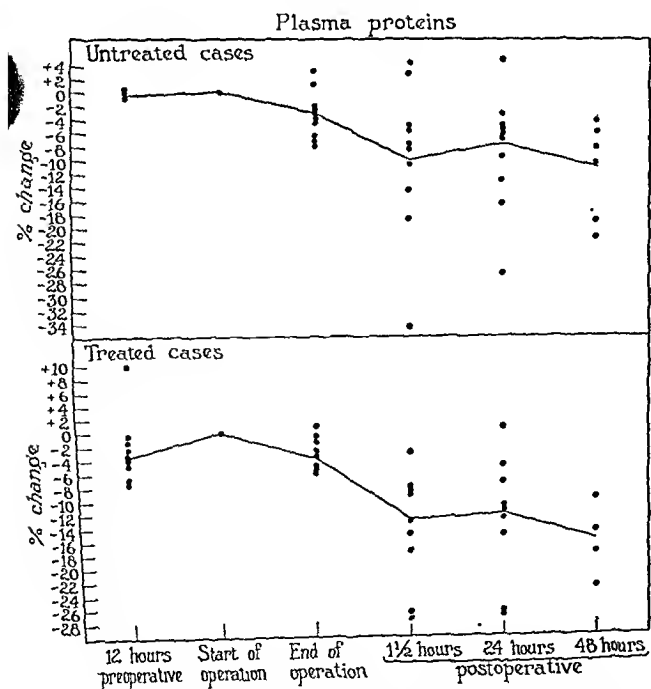


Fig. 2. CHANGES IN PLASMA PROTEINS. As with hematocrit values, determinations of plasma proteins showed a tendency to fall postoperatively. There were no significant differences in changes of plasma proteins in the treated and untreated groups. See legend for figure 1.

in the plasma did not change significantly until the 24-hour sample, when a fall in concentration of the order of 4% was encountered with considerable consistency. Although the decrease was small, the consistency with which it occurred appeared significant. It occurred regardless of the presence or absence of the symptoms of shock and appeared to be unrelated either to the quantity of the salt solution administered or to the amount of electrolytes excreted in the urine. In two cases in which the fall did not occur (cases 16 and 17) the 24-hour sample of blood was drawn too soon after an intravenous injection of NaCl for the figures to be of much value.

During the operation the concentration of K (fig. 5)

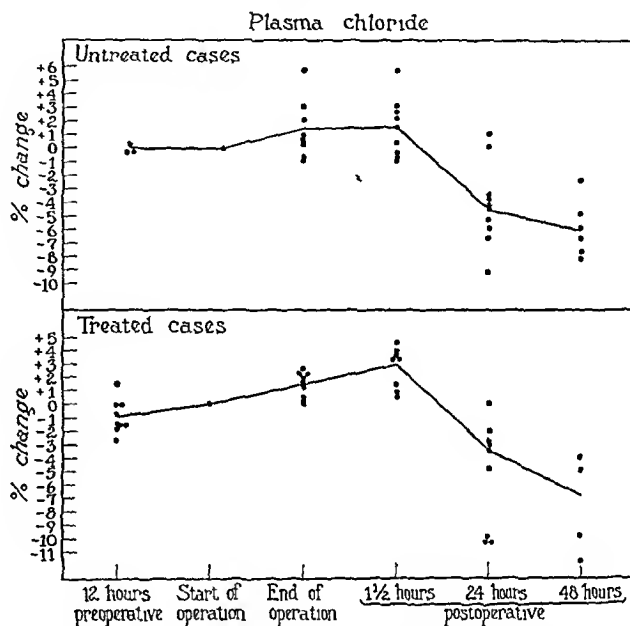


Fig. 3. CHANGES IN PLASMA CHLORIDES. The values obtained for plasma chlorides 1 1/2 hours after operation were in the aggregate slightly higher in the treated than in the untreated series. This difference appears too small to be significant and in all other respects there are no differences between the two groups. See legend for figure 1.

in the plasma in the control cases decreased to 6 to 30% and usually did not fully regain the preoperative level for 24 hours or longer. This decrease has been reported previously and has been attributed to the effect of the anesthetic in depressing the metabolic rate.

The nonprotein nitrogen content (fig. 6) of the plasma in the control series did not change significantly in the specimens obtained during the operation, at its end or one and a half hours later. In the specimens obtained 24 hours after the operation there was a large rise (30 to 80%) in some cases but there was no rise or even a fall in others. When the clinical data were examined with regard to these findings, the cases were found to fall into three groups. Among the pa-

tients who had not received fluids intravenously during operation there was a significant elevation of the N.P.N. content of the plasma at the end of 24 hours. Among the patients who had received intravenous therapy during or immediately after the operation, only those among whom shock symptoms subsequently occurred showed a significant increase in plasma N.P.N. 24 hours after operation. Both these groups also exhibited diminished output of urine during the first 24 hours after operation. Among patients who had received intravenous fluids during operation and did not exhibit symptoms of shock or fall of blood pressure after operation there was a consistent absence of a significant rise in N.P.N. content of the blood. It therefore appears likely that elevation of the nonprotein nitrogen content of the plasma 24

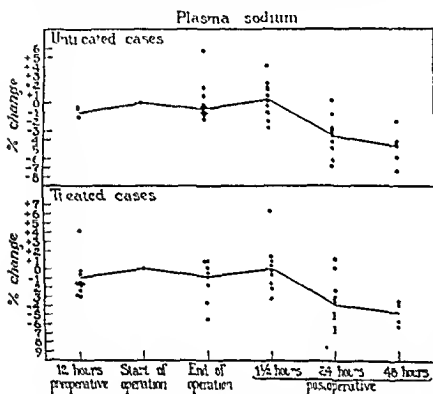


Fig. 4 CHANGES IN PLASMA SODIUM. As in the case of changes in plasma chloride, values for plasma sodium 24 hours after operation averaged 4% less than control values at the start of operation. There were no significant differences between treated and untreated groups. See legend for figure 1.

hours after operation represented transient renal impairment possibly related to an inadequately restored blood volume.

The changes observed in the concentration of Na, Cl and N.P.N. in the plasma were in the direction noted in acute adrenal cortical insufficiency, although they did not occur at the time when symptoms of shock were most likely to be present. The changes in the plasma K and in the concentration of the blood were not in the direction observed in acute adrenal cortical insufficiency. Nevertheless, if these changes could be abolished by the administration of desoxycorticosterone acetate, one might still assume that the former values represented in fact a 'mild' or 'sub-clinical' degree of adrenal cortical insufficiency resulting from the noxious stimuli of the operation and

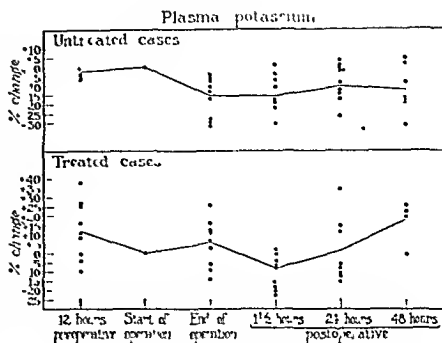


Fig. 5 CHANGES IN PLASMA POTASSIUM. In the untreated group there was a consistent fall in plasma potassium during operation. Preoperative administration of desoxycorticosterone acetate produced in most cases a decided fall in plasma potassium before operation, so that the 'control' determination at the start of operation represents in most instances a subnormal value for potassium. Instead of a further drop of potassium during operation in these cases there was a rise during operation with a subsequent postoperative fall to values in most instances even lower than the 'control' values. See legend for figure 1.

anesthesia. However, administration of desoxycorticosterone acetate did not abolish these changes. The changes in the blood of the patients in the group treated with desoxycorticosterone acetate were in

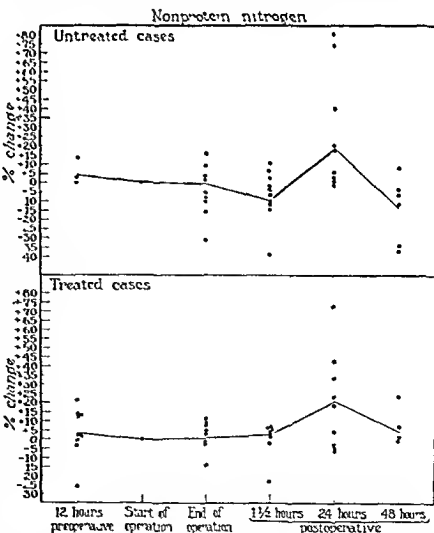


Fig. 6 CHANGES IN PLASMA NON-PROTEIN NITROGEN. There were no significant differences in the changes of plasma nonprotein nitrogen in the treated and untreated groups. See legend for figure 1.

most respects identical with those encountered in the patients in the control group and graphs of the two series cannot be distinguished one from the other.

The concentration of K in the plasma was the only determination whose behavior appeared different in the treated and the untreated group. In the blood sample obtained just prior to the operation and after the administration of desoxycorticosterone acetate there was in nearly every instance a rather conspicuous fall in the plasma content of K to levels which were less than or at the lower limit of the normal range, as compared with the normal values obtained the night before the operation. In the first patient, treated with the Perla regimen, a preoperative K level of 12.9 mg. per 100 cc. of plasma was obtained. In the control series, on the other hand, a significant change in K did not occur overnight before the operation. The concentration of K in the plasma of the treated patients generally rose from a subnormal level before operation to a relatively normal value during the operation, falling thereafter to the previous low level and not returning to the pretreatment level for as long as 48 hours. It seems fairly clear that this effect is directly due to the administration of desoxycorticosterone acetate. It is possible that such a depression of the concentration of K in the plasma to less than the physiologic level might have a deleterious rather than a beneficial effect, although symptoms which might be attributed to low plasma K were not observed in these patients.

In short, the changes of the constituents of the blood in the treated series do not show any essential differences as compared with those in the control series except in the case of plasma potassium and this might as readily be considered injurious as beneficial.

Factors influencing the urinary excretion of water, chloride and sodium varied so widely as to make extremely hazardous any further conclusion based on these data.

#### SUMMARY

The effect of the preoperative administration of desoxycorticosterone acetate to 9 women undergoing radical mastectomy for carcinoma of the breast has been studied by means of detailed clinical observations and chemical analyses of the blood and urine. Ten additional and similar cases were studied in the same manner, but without administration of desoxycorticosterone acetate, and serve as controls.

In 6 of the control cases a fall of blood pressure to 'shock levels' accompanied by shock symptoms occurred during operation and in 2 of these 6 cases a

second prolonged period of low blood pressure followed the operation. Despite ample clinical signs of shock, in no instance was elevation of the hematocrit value, total concentration of protein in the plasma or specific gravity of the plasma encountered. Instead, a decrease in these values was encountered in every instance during and after operation regardless of the condition of the patient or level of the blood pressure. Concentrations of the chemical constituents of the blood during and after the operation were remarkable chiefly for their constancy. A slight decrease in concentration of potassium in the plasma during the operation and a small but consistent decrease in concentration of chloride and sodium in the plasma after 24 hours were the most constant findings. In some cases there was a conspicuous increase of nonprotein nitrogen in the plasma after 24 hours. The changes in concentration of Na, Cl and N.P.N. in the plasma after 24 hours were in a direction which was compatible with acute adrenal cortical insufficiency and these changes therefore might be expected to prove amenable to correction by administration of desoxycorticosterone acetate.

In 6 of the patients treated with desoxycorticosterone acetate preceding the operation a fall of blood pressure to shock levels occurred during operation and in 2 of the 6 a second prolonged period of low blood pressure followed operation. The changes in the composition of the blood of the treated patients were identical with those encountered in the control series with the exception of the concentration of K in the plasma. This value usually was depressed to less than normal levels after administration of desoxycorticosterone acetate, in some instances to an extent which might be regarded as serious.

The results of this study do not provide any evidence for the hypothesis that shock as it is encountered among surgical patients is associated with acute adrenal cortical insufficiency and do not support the assumption that the preoperative administration of desoxycorticosterone acetate will prevent the appearance of surgical shock.

#### REFERENCES

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2. SELYE, H., C. DOSNE, L. BASSETT, AND J. WHITTAKER: On the therapeutic value of adrenal cortical hormones in traumatic shock and allied conditions. *Canad. M. A. J.* 43: 1. 1940.
3. WILLSON, D. M., M. H. POWER, AND E. J. KEPLER: Alkalosis and low plasma potassium in case of Cushing's syndrome: a metabolic study. *J. Clin. Investigation* 19: 701. 1940.

# ASSOCIATION NOTICE

## Announcement of the Annual Meeting

THE TWENTY SIXTH ANNUAL MEETING of The Association for the Study of Internal Secretions will be held in Atlantic City, New Jersey on Monday and Tuesday, June 8th and 9th, 1942. The Hotel Traymore will be the headquarters for registration and for the scientific and business sessions. Room reservations should be made early with the Hotel Traymore.

The Chairman of the Local Committee is Dr. Matthew Molitch, 705 Pacific Avenue, Atlantic City, New Jersey.

### PRESENTATION OF PAPERS

1 The title of the paper, and a comprehensive abstract must reach the President, Dr. Edgar Allen, 333 Cedar Street, New Haven, Connecticut, not later than April 10, 1942.

Abstracts submitted should be in proper form for printing in the program. Not more than the first 200 words can be included in the printed abstract.

2 Non members who wish to present papers must have their titles and abstracts introduced by members.

3 The abstracts of papers will be considered by the program committee and the final program announced about May 10th, 1942.

4 Papers will be limited to ten minutes for presentation. A ten minute presentation is designed for condensed discussion of new investigations, either in laboratory or clinical phases of endocrinology. Previous publication or presentation before other societies of national membership may be cause for omitting a paper from the program.

5 Papers presented at the Annual Meeting may be submitted for publication to the Editor of *ENDOCRINOLOGY* or *THE JOURNAL OF CLINICAL ENDOCRINOLOGY*. Such submission is invited. Acceptance of a paper for the program does not necessarily mean its acceptance for publication.

You are invited to bring this announcement to the attention of your colleagues and associates who have endocrine research in progress.

### NOMINATION OF OFFICERS

The By-Laws of the Association provide that nominations for all elective offices shall be made by a Nominating Committee and forwarded to the Secretary at least sixty days before the annual meeting. The Nominating Committee for the current year, appointed by the President and accepted by the Council, is as follows:

Dr. Earl T. Engle, *Chairman*, College of Physicians and Surgeons, 630 West 168th Street, New York City.

Dr. E. L. Sevringhaus, *Wisconsin General Hospital*, Madison, Wisconsin.

Dr. E. C. Kendall, 627 Eighth Avenue, S. W., Rochester, Minnesota.

The By Laws also provide (Article V, Section 2) that "Any member of the Association may submit nominations to the Nominating Committee for its consideration." Nominations may be sent to the chairman, Dr. Earl T. Engle, before March 1st, 1942.

The terms of the following officers expire at the time of the annual meeting in Atlantic City in 1942.

*President Elect*

*Vice-President*

*Secretary-Treasurer*

E. Kost Shelton

E. M. K. Geiling

Henry H. Turner

*Council Members*

David P. Barr

John C. Burch

E. C. Kendall

*Publication Board*

David P. Barr

Oscar Riddle

### THE E. R. SQUIBB & SONS AWARD

The E. R. Squibb & Sons award of \$1,000.00 was established in 1939, and given first in 1940 to Dr. George W. Corner, and in 1941 to Dr. Philip E. Smith. A special committee of five members of the Association chooses an investigator or investigators in the United States or Canada for one of the best contributions to endocrinology. Nominations for the award in 1942 by members of the Association may be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, not later than March 1st. The nomination should be accompanied by a statement concerning the nominee's contributions to endocrinology and a bibliography of his most important publications.

Edgar Allen, *President*

Henry H. Turner, *Secretary*

# CURRENT CLINICAL LITERATURE

Editor: HANS O. HATERIUS. Collaborators: E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, ARTHUR GROLLMAN, E. C. HAMBLIN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. C. PFEIFFER, GEORGE W. THORN, EMMERICH VON HAAM.

## BOOK REVIEWS

*Essentials of Endocrinology.* ARTHUR GROLLMAN. J. B. Lippincott Company, Philadelphia, 1941. Pp. 480.

The author sets out to select and expound the most significant and best substantiated data from the literature of endocrinology. Both laboratory and clinical data are incorporated. Such a task necessarily involves much arbitrary exclusion. In general excellent judgment has been shown in the process. The author is somewhat inclined in individual instances, however, to over-rate negative evidence as opposed to positive. Thus antihormones are dismissed as non-existent. Similarly, he sticks to his guns that the adrenal cortex produces only one hormone despite the fact that a victim of adrenal virilism may die of Addison's disease or that the urine of those harboring adrenal tumors may yield a variety of different active androgenic or estrogenic agents. However, such questionable items bulk but small in the total mass of information and the book as a whole is worthy of commendation for its succinct inclusiveness.

The subject matter is logically arranged and not difficult to read. The illustrations, which are mostly original, are well selected and satisfactorily reproduced. The format is pleasing. The book will be a welcome addition to the libraries of those who desire a not-too-technical and not-too-extensive introduction to the field of endocrinology.

*Annual Review of Physiology.* Ed. JAMES MURRAY LUCK. Volume 3, 1941, Annual Reviews, Inc., Stanford University, California. Pp. 784.

Increasingly scientists are coming to rely upon the Annual Review for rapid and reliable orientation toward recent developments in the broad field of physiology. The general excellence of previous volumes is maintained in this, the third. The greater space given to endocrine topics in this volume has permitted more adequate review than in the past.

Among the chapters of special interest to endocrinologists is that of E. C. Palmer and A. Ciocco on Growth. The topic is treated from an anthropological point of view but includes the outstanding publications on both human and animal subjects. The over-all rather than meticulously detailed significance of the work reviewed is presented.

E. H. Sheehan's section on the autonomic nervous sys-

tem includes discussion of the secretory innervation of the chief endocrine organs as well as the pharmacology of adrenin.

S. Soskin's thoughtful chapter on metabolic functioning of the endocrine glands throws into striking relief the multifarious confusion which, at this transition period, characterizes the field.

O. Riddle discusses succinctly and informatively recent work on endocrine aspects of the physiology of reproduction. This field, too, is shown to afford relatively few consistent and adequately inclusive generalizations.

M. H. Friedman's chapter on reproduction in mammals is notable for the emphasis upon the necessity for more sophisticated control of environmental variables and for the philosophical search for rationale in explaining both concordances and discordances in existing evidence.

*The Art and Science of Nutrition.* ESTELLE H. HAWLEY and GRACE CARDEN. The C. V. Mosby Company, St. Louis, 1941. Pp. 619.

Nutrition is no longer a mere matter of meal planning, based upon the meager knowledge or ability of the housewife. Recognition of the role which nutrition plays in clinical medicine has become increasingly apparent and it is with the realization of the need for scientific knowledge of food and its uses, and of disease and its metabolic consequences, that the authors have outlined in this text the principles of normal nutrition and have indicated when, why, and how modifications of the normal diet may be necessary.

While the book has been written chiefly for those interested in the theory and application of nutrition it contains important information for the general practitioner and the specialist.

In chapter VI "The Endocrines and Their Role in Nutrition" the authors state "while at first thought a discussion of the endocrines, those organs which secrete powerful regulating substances into the blood, is outside the realm of nutrition, their hormones are important factors influencing the structural and nutritional conditions of the body and should be mentioned briefly." In addition to this chapter on the endocrines there are other chapters of special interest to the endocrinologist: "Nutritional Needs in Pregnancy"; "Complications in Pregnancy"; "Lactation"; "Diabetes Mellitus"; "Hypoglycemia or Hyperinsulinism"; and "Addison's Disease."

The book is attractively written and presented, with

carefully prepared diet prescriptions for normal and therapeutic needs. Many illustrations depict the more interesting and important phases of the subject matter and support the material presented in a clearly defined manner.

**Simplified Diabetic Manual** ABRAHAM RUDY, M. B. Rows & Company, Inc. 2nd Ed. New York. 1940. Pp. 216.

The second edition of this book carries out the same purpose as the original, bringing the subject up to date, and giving special attention to the problems arising from the use of new types of insulin.

The role of heredity and other factors in the development of diabetes are discussed and the prevention and treatment of various complications are taken up in the light of their importance.

The importance of diet in the treatment of diabetes is emphasized and 163 recipes for American, Jewish, French, German, Italian and Armenian dishes are given, so that normal food habits may be followed whenever possible.

**Natural Resistance and Clinical Medicine** DAVID PERLA and JESSIE MARIONSTON. Little, Brown and Company, Boston, 1941. Pp. 1344.

In this work the authors have analyzed the various factors that determine or modify natural resistance and susceptibility, in relation to their importance in general physiology. The earlier knowledge of natural resistance or natural immunity was included under the old term "constitution" and dates back to antiquity. Modern knowledge of acquired immunity owes its origin to bacteriology and it was not until acquired immunity could be clearly separated from natural resistance and until endocrinology could demonstrate the hormonal basis for many of the manifestations of constitution that an adequate basis could be provided for the scientific investigation of natural resistance.

The remarkable progress of endocrinology over the past three or four decades has provided a sound hormonal background for the older anatomical, physiological and pathological manifestations of constitution.

Sections III and IV of the book are of special importance to the endocrinologist. Section III deals with the major topic of sex and resistance and Section IV takes up the role of other endocrine glands in resistance.

Each Chapter is summarized and very complete bibliographies have been included at the end of each chapter.

## ADRENALS

NEWBURGER, R. A.

Effect of desoxycorticosterone acetate on hypochloremia in pneumonia. *J. Lab. & Clin. Med.* 26: 1642. 1941.

Desoxycorticosterone acetate (1) in sesame oil, administered intramuscularly in doses of 10 to 20 mg. per day seemed of no benefit to 3 pneumonia patients who had serum chloride concentrations of 95 mEq per l. or less. Ten mg. of 1 had no effect upon the serum chloride level and with 15 to 20 mg. the results showed a moderate rise,

however, as striking a rise took place in 1 patient who had received only 6 g. of NaCl daily and no 1. These patients were also under treatment with sulfonamide derivatives.—H. W. Robinson (Courtesy Chem. Abstracts)

LOEB, R. F.

Problems of adrenal insufficiency. *California & West Med.* 55: 61. 1941.

The development of hypotension (which may reach extraordinarily low levels in the crises) is in part to be attributed to the disturbance of salt and water metabolism. The second physiological disorder in adrenal insufficiency is abnormal carbohydrate metabolism (hypoglycemia). Adrenal cortical extract might act as "anti-insulin." Adrenalectomized animals show a lessened work capacity. There also may be a disturbed vasomotor system. There are now more than 20 steroids isolated from the adrenal glands in crystalline form. There are 3 therapeutic agents now available in the treatment of adrenal insufficiency: desoxycorticosterone acetate, adrenal cortical extracts, DCA. DCA has no demonstrable effect on carbohydrate metabolism and its effect on pigmentation is doubtful. Cortical extract has but little to recommend in correction of salt and water disturbances but might help carbohydrate metabolism slightly. Ultimate solution of the "exhaustion states" must be left to the future.—M. L. Hsley (Courtesy Biol. Abstracts)

RHIND, E. G. G., AND A. WILSON.

Diabetes mellitus in Addison's disease. *Lancet* 37: 39. 1941.

A case of Addison's disease is described in the course of which diabetes mellitus developed. Autopsy revealed atrophy of the suprarenal glands and of the islets of Langerhans. The pathological changes suggest that there is no relationship between the number of basophil cells in the anterior lobe of the pituitary and the blood sugar level.—Courtesy Clin. Abstracts

THELANDER, H. E., AND M. CHOLFFIN.

Neonatal cortical insufficiency (Addison's disease) associated with the adrenogenital syndrome. *J. Pediatr.* 18: 779. 1941.

Symptoms are divided into those produced by adrenal cortical insufficiency and by excess androgen production. The former parallel those of Addison's disease in adults, including anorexia, vomiting, diarrhea, weakness, anuria, rapid pulse, cyanosis, and extreme dehydration. Pigmentation changes are occasionally described. Death may occur in convulsions, in collapse with low temperature, extreme weakness and coma, or in marasmus. The second group of symptoms is due to hypersecretion of androgen, which in the female produces masculinization and pseudohermaphroditism. Effects in the male are not so obvious at birth. After the first months, however, the penis is noticeably enlarged, pubic hair appears, the voice deepens and advancement in bone age occurs. The testes may not be large. Only one case has been studied pathologically, in which the adrenals showed bilateral, marked cortical



hypertrophy. The acute case should receive salt subcutaneously, intravenously, or both, and glucose solution may be given intravenously with normal saline. Percortin (DCA) should be administered hypodermically. After chemical balance has been established, treatment should be regulated to meet the individual need. When DCA is given, salt should be moderately restricted. A normal amount of dietary K is indicated. The advisability of surgical approach is doubtful. Ultimate prognosis of cases carried from infancy on hormones or DCA is not known.

—*Courtesy Clin. Abstracts.*

## ENDOCRINE GENERAL

STRASSMANN, E. O.

Endocrine treatment of masculine hairgrowth in women. *J. Internat. Coll. Surgeons* 4: 137. 1941.

Endocrine therapy in a patient with amenorrhea and polyglandular disturbance of the andropituitary type unexpectedly caused the disappearance of heavy masculine hairgrowth on the face, trunk and extremities. Nine additional cases of hirsutism combined with menstrual disorders were treated. Seven of these showed similar reactions lasting as long as the substituted hormones were effective. The dosage and timing of hormones in this treatment followed the natural cycle as closely as possible. Estrogens and gonadotropins were limited to the first and second postmenstrual weeks. During the third week only progesterone was given. One course of this type demonstrates whether the hirsuties are influenced or not; long drawn out treatments without results can thus be avoided. Since most patients with hirsuties have some type of menstrual disorder, improvement of these complaints can be expected. The use of additional thyroid tablets is beneficial in instances of low basal metabolic rate. It is pointed out that endocrine therapy for masculine hairgrowth in women is in its earliest infancy and that, for the time being, results are unpredictable and only temporary.—*Courtesy Clin. Abstracts.*

## HYPOPHYSIS

PAYNE, F. L.

Hormone studies in the presence of hydatidiform mole and chorionepithelioma. *Surg., Gynec. & Obst.* 73: 86. 1941.

Eight moles and 5 chorionepitheliomas are reported with regularly spaced hormonal titrations for identification and prognostication. Demonstration of increments in values over a short period of observation are the most valuable criteria used by the author, with microscopic study of curetted tissues and finally the clinical picture in decreasing order of importance. Four types of molar activity are described: first, the actively growing tumor with marked prolactin concentrations; regression with normal or slightly elevated prolactin excretion; thirdly, an encapsulated or degenerating mole with decreasing prolactin titre and, lastly, the missed molar abortion with less prolactin concentration than that of normal pregnancy.—R. A. Lyon (*Courtesy Biol. Abstracts*).

SINGER, E.

The hormonal antigens of the anterior pituitary gland. *Australian J. Exper. Biol. & M. Sc.* 19: 125. 1941.

The antigenic properties of hormonal fractions isolated from pituitary glands were compared with analogous fractions from ox kidney. The same antigens were found in both. Observations are presented on antigens other than those associated with the known hormonal fractions, and on the influence of carbohydrate and lipid components on the antigenicity of the pituitary gland.—E. Eagle (*Courtesy Chem. Abstracts*).

WESTMAN, A.

Urinary prolactin in hyperemesis gravidarum. *Acta obst. gynec. Scandinav.* 20: 203. 1940.

Increased prolactin levels were found in the urines of most of 28 patients, but no correlation between the increase and the severity of the condition was observed.—M.M.R. (*Courtesy Chem. Abstracts*).

WOODWARD, F. R., AND R. J. MAIN.

Gonadotropin excretion during the menstrual cycle. *Virginia M. Monthly* 68: 530. 1941.

The urinary gonadotropin of a woman 25 years old who was taking thyroid regularly, was determined over two 30-day periods. The amount of hormone excreted was marked and irregular. Similar results were obtained when using the first morning or the 24 hour specimen of urine. No correlation of gonadotropin excretion with intercourse was found.—R. J. Main (*Courtesy Biol. Abstracts*).

## PANCREAS

MAGNER, W.

Hyperinsulinism: a report of 2 cases. *Canad. M. A. J.* 45: 49. 1941.

Two cases of hyperinsulinism are reported. In the first case operation revealed a single islet adenoma which was removed with great ease. In the second case no tumor nodule was found; the body and tail of the pancreas were excised. Following the operation both patients were completely relieved of hypoglycemic symptoms.—*Courtesy Clin. Abstracts.*

MELLINGHOFF, K., AND G. VOGES.

Action of depot insulin in normal subjects. *Deutsches Arch. f. klin. Med.* 185: 345. 1939.

Forty  $\mu$  of various depot insulins and of insulin were injected into normal subjects maintained on a standard diet. Hypoglycemia occurs as rapidly with depot insulin as with ordinary insulin.—B.C.P.A.

## THYROID

ABRAMSON, D. I., AND S. M. FIERST.

The peripheral vascular response to exercise in the hyperthyroid state. *J. Clin. Investigation* 20: 517. 1941.

The rate of blood flow in the forearm was determined

by means of the venous occlusion plethysmographic method. The blood flow repayment following exercise was much greater in the hyperthyroid state than in the period following subtotal thyroidectomy. A correlation was apparent between the level of  $O_2$  consumption and the magnitude of the excess blood flow elicited by the exercise. Exercise placed a much greater load upon the circulation in hyperthyroidism than in the normal state — *D I Abramson*

#### BAINBRIDGE, W S

The toxemias and the thyroid gland. *J Internat Coll Surgeons* 4 233 1941

Illustrative cases are cited in which the relief of somatic factors, with or without operation on the gland itself, cured some pathologic conditions of the thyroid. It is concluded that certain conditions of the thyroid gland are due to foci of infection at distant points. Toxic irritation in the blood affects the cells, thus the activity of the gland may either be augmented or diminished, or the character of its secretion changed. One of the many causes of thyroid pathology is chronic intestinal toxemia. A goiter whose size diminishes and whose accompanying symptoms disappear after surgical or therapeutic measures on the intestinal tract (or other suspected source of infection) is undoubtedly caused by the absorption of that particular toxin — *Courtesy Clin Abstracts*

#### BASSETT, A M, A H COONS AND W T SALTER

Protein bound iodine in blood. V. Naturally occurring iodine fractions and their chemical behavior. *Am J M Sc* 202 516 1941

The protein bound I in blood plasma of man and of animals resides chiefly in the traditional albumin fraction. This I is subject to fluctuations dependent upon thyroid activity. Such fluctuations, in absolute terms, are due chiefly to a thyroxine like moiety. The moiety resembling diiodotyrosine might increase proportionately, but it contributes relatively little to the absolute change from the normal level. Accordingly, total protein bound I fluctuates largely with thyroxine like I. In myxedema, the thyroxine-like fraction practically disappears. Despite variations in this protein bound I, the ionized I (inorganic) was rather low and approximately constant regardless of the state of thyroid activity. Nevertheless, it increased markedly when extraordinary, though perhaps very small, amounts of I entered the organism. Simultaneously a false increase in the protein bound I occurred which could be reproduced by the addition of iodide to plasma in vitro. The protein bound thyroxine like moiety of the plasma I is a good objective index of circulating thyroid hormone. Plasma protein bound I might be used clinically to confirm physiologic thyroid status — *W T Salter*

#### Buño, W

Pseudotuberculous follicles in goitres (Formaciones pseudotuberculosas en los bocios). *Arch Soc de biol de Montevideo* 10 26 1940

Pseudotuberculous follicles without caseosis and with

no tendency toward progressive development are described. The author believes that they are formed by cells of conjunctive tissue origin, because it was observed that the connective tissue buds into vesicles, and because of the behaviour toward blood pigment — *J E Mackinnon (Courtesy Biol Abstracts)*

#### CUTLER, E C, AND S O HOERR

Total thyroidectomy for heart disease. A five year follow up study. *Ann Surg* 113 245 1941

A 5 year follow up study is presented of 57 consecutive cases of total thyroidectomy performed for heart disease during 1932, 1933 and 1934. The majority of the patients had been unrelieved by medical therapy and presented a serious operative risk. There were 12 five year survivors in the group of 32 with angina pectoris, and 4 five year survivors in the group of 25 who had congestive failure. There were 5 postoperative deaths, 4 of these, as well as all but 3 of the later deaths, were attributable to heart disease. The best results were obtained in patients with angina pectoris. Twenty six of the 27 patients surviving more than 6 months were relieved of pain in some degree for six months or longer, and 8 of the 12 five year survivors had sustained relief. Preoperative evidence of congestive failure or cardiac enlargement was an unfavorable prognostic sign for long survival. In congestive failure the 5 year results were disappointing. Fifteen of the 25 patients lived for 6 months or more, and 12 of these had relief for 6 months or longer. Of 4 five year survivors, 3 showed sustained relief, 2 of these 3 have died of congestive failure in the sixth year after operation. Results were better in the group having congestive failure from chronic rheumatic valvular disease than from arteriosclerotic or hypertensive heart disease — *Courtesy Clin Abstracts*

#### KING, J D, AND F E HAMILTON

The iodine content of the normal human thyroid gland and its correlated histology. *West J Surg* 49 231 1941

An extensive survey of pertinent literature revealed marked variation in gross appearance, histological structure and I content of the normal gland. Glands from 'goitrous' regions average 45 to 63 g gm, I concentration 53 mg % dry weight, and possess the smallest follicles, highest % of epithelial proliferation and of nodule formation. Glands from 'moderately goitrous' regions average 17 to 37.5 gm, I concentration 84 mg % dry weight, and are medium and moderate as to epithelial proliferation, size of follicles and incidence of nodule formation. Glands from non goitrous regions average 12.5 to 25 gm, I concentration 234 mg % dry weight, and show the largest follicles, lowest % of epithelial proliferation and lowest incidence of nodule formation. An extensive bibliography is appended — *H O H*

#### LIGHTMAN, S S

Liver function in hyperthyroidism, with special reference to the galactose tolerance test. *Ann Int Med* 14 1199 1941

Employing various clinical liver function tests, 45 to

90% of cases of hyperthyroidism show some functional impairment, usually of slight to moderate degree. Results of the galactose tolerance test may be most uniformly correlated with clinical criteria of severity of thyrotoxicosis, e.g., weight loss, duration of the disease, and B.M.R. Other tests show poor correlation or none. Factors which may directly improve impaired liver function are administration of I and partial or subtotal thyroidectomy. Normal function may be restored. On the other hand, upper respiratory infections and other infections may aggravate existent liver function disturbance even in absence of fever. A mechanism for the hepatic function derangement in hyperthyroidism is suggested based upon loss of a protective factor in the depletion of liver glycogen.—H.O.H.

McGREGOR, J. K.

Recurrent hyperthyroidism. *J. Internat. Coll. Surgeons* 4: 239. 1941.

Theoretically, nodular-toxic goiters should not recur following operation, provided that practically total thyroidectomies were done. Nevertheless, at least 25% of the author's cases of diffuse toxic hyperthyroidism have shown some signs of recurrence. The greater the urge from without the thyroid, the more chance there is of a recurrence; in other words, polyglandular types recur in spite of complete operation. The author believes that recurrent hyperthyroidism is regional, as is the severity of the disease. Recurrences are treated by iodine, which may be necessary for the remainder of the patient's life. Secondary operations should be left until all other methods have been tried. Radiation of the thyroid gland is always used as a preliminary measure, and radiation of the suprarenals and pituitary has been recently used with satisfactory results.—*Courtesy Clin. Abstracts.*

RIGGS, D. S., E. F. GILDEA AND E. B. MAN.

The clinical interpretation of blood iodine levels. *Connecticut M. J.* 5: 209. 1941.

In clinical hyperthyroidism the blood I was elevated; in most instances the level was 2 to 6 times the highest normal quantity. Patients with spontaneous myxedema or with postoperative hypothyroidism had blood I values well below the normal range.—R. Berggren (*Courtesy Chem. Abstracts*).

RIGGS, D. S., E. F. GILDEA, E. B. MAN AND J. P. PETERS.

Blood iodine in patients with thyroid disease. *J. Clin. Investigation* 20: 345. 1941.

A reinvestigation of blood I in patients with thyroid disorders has been undertaken because it has been found that many of the older methods yielded erroneously high normal values. The blood I levels have been determined in 55 patients with a number of different symptoms and

signs of thyroid disorder. The results have been analyzed in an attempt to determine the relation of blood I to the symptoms and signs of hyperthyroidism. The level of blood I has been found to be closely related to thyroid activity. In 31 patients with hyperthyroidism the blood I ranged between 6.4 and 21.97%. In 7 patients with myxedema it varied from 0.3 to 1.77%. There was no overlapping with the normal range of 2.4 to 4.27% in 26 euthyroid subjects. Six patients with nodular goiters but without symptoms of thyroid overactivity had blood I which did not differ significantly from normal. Elevated blood I values are invariably found in hyperthyroid patients. However, certain patients without manifest hyperthyroidism may also have an elevated blood I.—*Courtesy Clin. Abstracts.*

SALTER, W. T., A. M. BASSETT AND T. S. SAPPINGTON.

Protein-bound iodine in blood. VI. Its relation to thyroid function in 100 clinical cases. *Am. J. M. Sc.* 202: 527. 1941.

A series of 100 cases of suspected thyroid disturbance and 10 control individuals has been analyzed from the standpoint of final clinical diagnosis, B.M.R. and plasma protein-bound I. When the first 2 of these criteria are in agreement, there is a close correlation between the plasma I and the B.M.R. Such cases amount to 71% of the entire group studied. Of the remaining 29%, the B.M.R. often did not clearly reflect the clinical status and the plasma protein-bound I proved much more reliable. This was particularly true in the group of "Graves' disease without hyperthyroidism" in which the B.M.R. ranged from -20 to +40%, but the plasma protein-bound I was normal. These data constitute additional evidence for the possible dissociation of physiologic hyperthyroidism and clinical Graves' disease. In hypothyroidism, plasma protein-bound I is a highly reliable criterion for confirming lack of thyroid hormone, even when full-blown myxedema is absent. The simplified chemical procedures employed are partly empirical. Their use is justified by their consistency with clinical data, but due care should be exercised in comparing the data with the results obtained by other methods.—W. T. Salter.

SHERRILL, J. W., AND E. M. MACKAY.

Hypothyroidism and bladder function; an experimental study. *J. Urol.* 46: 34. 1941.

Atony of the bladder observed in patients suffering from hypothyroidism stimulated an experimental study of the relation of these conditions in the albino rat. Hypothyroid rats regularly showed bladder atony as measured by the filled area shown by a radio-opaque compound in urine-bladder emptying time and the lowered ability to sustain an artificial increase in the intra-bladder pressure.—*Authors' summary.*



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## Simmonds' Disease

A Clinical Study with Review of the Literature; Differentiation from Anorexia Nervosa by Statistical Analysis of 595 Cases, 101 of Which Were Proved Pathologically<sup>1</sup>

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## [[Hypophyseal Cachexia]]

THE HISTORICAL SEQUENCE in the development of knowledge concerning a disease usually follows a fairly constant pattern. First an author of exceptional discernment reports one or several cases with a group of symptoms or pathological findings which in his opinion justify the postulation of a new syndrome. Subsequent authors add similar cases and further observations, and, as the general experience widens, more complete and precise information concerning the disease is accumulated. In the course of time the suggestion is made that the original author's name be used in designating the disease. Such tribute to an original concept seems altogether fitting and at the same time furnishes a historical perspective. Diverse opinions concerning the necessary

criteria for diagnosis are expressed. Therefore a periodic critical review of the accumulated knowledge is of considerable value in clarifying and appraising these varying points of view.

Thus, it was Morris Simmonds (1855-1925) (1), pathologist of the University of Hamburg, who in 1914 first suggested that the clinical syndrome now known as hypophyseal cachexia was due to severe pathologic interference with the function of the adeno-hypophysis. The diagnosis in the original report was based upon findings at autopsy. Four years later Nonne of Hamburg (reported by Bostroem, 2) made the first diagnosis in a living patient, this diagnosis was later verified pathologically and reported by both Simmonds (3, 4) and Bostroem (5).<sup>2</sup> The first proved case in which attention was called to a low basal metabolic rate was that of Monakow (7) in 1922. During the same year Lichtwitz (8) first used the designation

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<sup>2</sup> Presented in summary before the Annual Meeting of the Association for the Study of Internal Secretions, San Francisco, June, 1938.

<sup>2</sup> Leschke (6) claimed the distinction of being the first to diagnose hypophyseal cachexia during life.

'Simmonds' disease' in the title of his publication.

Since then, many cases have been reported in the literature and varying views have been expressed concerning the syndrome. This diversity is due in part to the fact that quite typical cases are seen occasionally without pathological changes in the pituitary body. The reverse is also true, namely, destruction of the pituitary may be complete without the usual clinical picture of hypophyseal cachexia; for instance, obesity rather than emaciation may occur. Further confusion is caused by the observation that in rare instances a case of Addison's disease may simulate Simmonds' disease. However, the greatest confusion is brought about by the disturbing experience that true anorexia nervosa, originally described by Gull in 1868, may simulate hypophyseal cachexia in every important detail.

These perplexities have led to many errors in diagnosis so that the time seems ripe for a comprehensive review and an analysis of the available facts concerning the disease. This purpose would seem to be accomplished best by a critical study of the details of previously reported cases. Therefore, the literature has been surveyed as completely as possible up to January 1940 and a few cases have been added after this date.<sup>3</sup> With rare exceptions, each article has been consulted in the original publication in an attempt to eliminate the repetition of errors made in previous comprehensive summaries, and the consideration of the same case more than once.

### Synonyms

It will be recalled that when Cushing published his first article on 'pituitary basophilism,' he included cases from the earlier literature published under other designations which he regarded as characteristic examples of the new syndrome. We have likewise included in our analyses several cases published prior to 1914, such as the one of Ponfick, 1899 (9), which seem to us characteristic of Simmonds' disease. Extremely interesting in this connection is Sheehan's discovery of a group of cases reported in 1883 by Simpson (10) under the title, "Superinvolution of the uterus." Simpson found an incidence of 22 in 1300 patients (1.7%) with an average age of 30, many of whom had amenorrhea and 'wasting' which seemed to date from marked loss of blood at parturition. The data were not sufficiently detailed to warrant inclusion in our analysis, but it is altogether likely that

some of these were instances of true pituitary cachexia.<sup>4</sup>

In all likelihood the cases reported under the two designations, 'insuffisance pluriglandulaire' by Claude and Gougerot in 1907-1908 (14, 15, 16), and 'multiple ductless glandular sclerosis' by Falta (17, 18, 19) should really have been classified with Simmonds' disease and consequently are included in our data. At that time (early twentieth century) little was known of the manner in which the anterior pituitary, now frequently referred to as the 'master gland,' dominates the hormonopoietic system. Hirsch and Berberich (20), were the first to suggest that cases previously reported as 'pluriglandular insufficiency' might be instances of true Simmonds' disease. In 1928 Thür (21) suggested that Simmonds' disease and multiple glandular sclerosis were similar and might be related, and in 1938 Herrick (22) and Meyler (23) expressed the opinion that the two conditions were identical. The designation, 'pluriglandular insufficiency,' has also been used by Petschacher and Hönlinger (24), Zondek (25), Stenström (26), Usadel (27), Wachstein (28), and Lindemann (29). 'Multiple ductless glandular sclerosis' has been used after Falta by the following authors: Hochstetter (30), Lindemann (31), Kiyono (33), Dimmel (34), Lissner (35), Richter (36), Binggold (37), Liebers (38), Heinrichs (39), Umber (40), Rössle (41), Boller and Goedel (42), Dunn (43), Oyama and Otomo (44), Meerwein (45), and Priesel (46). What is known as progeria may be Simmonds' disease as it appears in younger people with emphasis on the symptom of premature senility; Rand in 1914 (47) suggested that pituitary disturbance may be chiefly responsible for this clinical syndrome.

Furthermore, certain cases that we regarded as sufficiently characteristic to include in our analysis were published under the following designations: 'Myxedema with testicular atrophy' (48); 'Myxedema or cretinism with pituitary changes' (9, 49, 50, 23, 51); 'Non-operative myxedema' (52); 'Operative myxedema' (53) (following removal of two hypertrophied breasts in a male); 'Acquired myxedema with sexual regression,' (54); 'Infantilisme reversif,' (55); 'Insuffisance endocrinienne thyroïd-testiculaire,' (56); 'Encocrine cachexia,' (57); 'Infantilisme tardif de l'adult,' (58, 59); 'Insuffisance pluriglandulaire interna thyro-testiculo-surrénale,' (60); 'Insuffisance diastémato spermatique acquise avec atrophie thy-

<sup>4</sup> Hun and Prudden (11) reported the case of a woman aged 54 who had mental derangement, terminal anorexia, diarrhea and emaciation; at autopsy atrophic fibrosis of the thyroid was found. The case was reported as 'Myxoedema.' Pituitary endocrinopathies were not known at that time and the atrophic fibrosis of the thyroid may well have been secondary to pituitary disease. There are many other cases in the older literature with clinical narratives suggestive of Simmonds' disease in which the end was fatal but the pituitary was not examined. Some of these were labelled anorexia nervosa because the authors were aware of this disease as described by Gull in 1868 (12, 13).

<sup>3</sup> Although the local library facilities, including the University of California Medical Library, the Lane Medical Library, and the Library of the San Francisco County Medical Society are extensive, some of the smaller foreign journals are not available. A few articles of particular interest were obtained through the mailing services of the New York Academy of Medicine and the Surgeon General's Library.

roidienne,' (61), 'Polyglandular, multiglandular or pluriglandular syndrome or disease,' (62-69); 'Myxedema,' (17, 70), 'Preadolescent hypopituitarism; posterior lobe insufficiency without anterior lobe involvement,' (71), 'Addison's disease with pluriglandular disturbance,' (72), 'Dystrophia cachectogenitalis,' (73, 74), 'Presenile involution,' (25), 'Senium praecox' (25); 'Thyrosexual insufficiency,' (75), 'Luetic cachexia,' (76); 'Spontaneous hypoglycemic coma,' (77), 'Cerebral Magersucht (thinness),' (78-81), 'Cerebral hypophyseare Magersucht,' (82, 83), 'Magersucht (thinness)' (84-86, 88-95, 29), 'Post partial Magersucht,' (96), 'Hypophyseal Magersucht or Margreuer,' (97-102), 'Hypopituitarismus totalis,' (103), 'As thenia gravis hypophyseogenica,' (104); 'Interrone insulare Syndrom,' (105), 'Primare Polynesie,' (105, 106), 'Hypophyseothrogenic emaciation,' (107), 'Hypophyseal thyrogeital syndrome,' (108), 'Late pubertal emaciation,' (109, 110, 111), 'Post partum emaciation,' (112); 'Non-myxedematous hypothyroidism,' (113); 'Hypopituitarism,' (114, 115)

The term, 'cachexia hypophyseopriva,' was first suggested by Elsberg and Krug in 1917 (116) and has been used frequently since then.

### Reviews

The most important collections of reported cases of Simmonds' disease were compiled by Léschke, 1919 (6), 21 cases,\* Graubner, 1925 (117), 34 cases, Tauber, 1927 (118), 10 cases (summarized in tabular form); Calder, 1932 (119), 70 cases, Silver, 1933 (120), 41 accepted cases, Howard and Rhea, 1936 (121), 71 cases, Robert, 1936 (122), 90 cases (with details presented in tabular form), and Van Balen, 1939 (123), 82 cases (of which the author accepts 22 as Simmonds' disease). Sheehan, 1939 (124), has tabulated a special group confined to cases of Simmonds' disease consequent to postpartum necrosis of the anterior pituitary. He analyzed 32 cases which were verified at autopsy and 19 cases which were typical clinically

### CLASSIFICATION OF CASES

In 1938 we (125) presented the observations made in eight cases which were considered typical clinical examples of Simmonds' disease. Of these, two patients had died and the clinical diagnosis of one was verified at autopsy. Subsequently (126) we published a short summary of a critical statistical study comprising 69 cases verified at autopsy and 134 typical clinical cases, most of the patients in the latter group were

\* Subsequently von Bergmann (87) altered his conception of allying the group of cases he had called 'Magersucht' to hypophyseal cachexia and considered them to be of psychogenic origin

All but two of the cases referred to by Léschke have been read in the original publications. Only 6 of these could be regarded as instances of Simmonds' disease and have been included in our analysis of verified cases (group A). It is only fair to state that Léschke's elaborate article was concerned primarily with pathological lesions involving the hypophysis or hypothalamus and their relation to diabetes insipidus. The 21 cases referred to include 3 of total destruction of the anterior lobe only and 18 of destruction of the entire pituitary body.

alive and in those who had died no pathological investigations had been made. In the present paper, the factual data upon which the previous one was based are considered far more comprehensively. Several new case records of patients seen by us personally have been added (see *Case Summaries* at the end of this paper), and in addition the details concerning certain unpublished cases seen by other physicians have been made available to us. Necessary additions to and rearrangements and reclassifications of cases account for any discrepancies which may have occurred in figures or percentages. Furthermore, we have considered in this paper, cases which we regard as suggestive rather than convincing examples of Simmonds' disease. For purposes of classification and comparison the eight groupings given below have been made. Under each group are listed bibliographic references to the literature on these cases. Within each set of parentheses are cited all of the references to an individual case. It will be noted that some cases have been reported more than once, by the same or by different authors. The references in each group are listed in chronological order.\*

### Group A. Typical Clinical Cases, with Pathological Verification

The 101 cases we have included in this group are those reported as follows: (9), (14, 15), (56, 60), (17, 133), (63), (1, case 1, 134, case 12, 4, case 1), (135, 64), (136, case 1, 137 case 1), (136, case 2, 137, case 2), (138), (139, 140, 4, case 2), (2, 5, 141, 3, 4, case 3), (4, case 4), (6), (142), (143, 144, case 1, 145 case 2), (146, 7), (147, case 8), (148, 30), (149, 150, 151, 152, case 1), (153) (154, case 24), (155, case 1, 65, case 1), (156, 25, case 4, 157, 158, case 2), (159, 25, case 2, 157, 33, case Vb, 148, case 10), (160), (161), (162), (25, case 5, 157, case 6, 158, case 6), (163, case 1), (164, case 1, 165, case 2, 166), (164, case 2, 165, case 1), (167), (20), (117), (168, 169), (34), (170), (171), (172, case 1), (77), (173), (174, case 7), (175), (21), (176, case 1), (177), (36), (178, case 1), (179), (180), (181), (182, case 1, 183, case 2), (182, case 2, 183, case 1), (182, case 3, 183, case 4), (184, case 1, 185, case 2), (186), (187), (188, case 2), (39), (189, case 1), (190), (191, case 3), (185, case 1, 86, case 4),

\* Extensive tables have been prepared, listing the cases in each of these groups and summarizing the following data for each case: sex, age, weight loss, asthenia, duration of amenorrhea, frigidity

For these detailed tables order Document 1604 from American Documentation Institute, Office of Science Service, 2201 Constitution Avenue, Washington D C remitting 75 cents for microfilm form

This case presents a Simmonds' like picture resulting from a destructive lesion of the pituitary body. Some may be inclined to question the diagnosis of Simmonds' disease and call it pituitary dwarfism with infantilism (and it was so regarded by Cushing). However, hypophyseal infantilism when produced by a suprasellar cyst or chromophobe adenoma is not as a rule associated with loss of weight and a very low basal metabolic rate. The presence of these two factors influences us to include this case as one of Simmonds' disease

(192), (41, case 3), (193, 194, case 2), (195), (132, case 11; 196, case 2; 197, case 3; 198, case 3), (42, case 1), (42, case 2), (69), (199), (200), (121), (201, 202), (109, case 1; 198, case 2; 110, case 1; 111, case 11), (109, case 2; 198, case 17; 110, case 3; 111, case 10), (203), (204), (205, case 1), (206), (45), (207), (125, case 2; 126, case 1), (208, case 1), (208, case 2), (209), (210, case 1), (210, case 2), (211), (212), (114, case 1; 115, case 1), (114, case 2), (114, case 3), (213), (214), (215), (216), (217), (present report, case 1).

### Group B. Typical Clinical Cases, without Pathological Investigation

The 158 cases included in this group are those reported as follows: (57, case 1), (61), (116), (71), (218, 219), (147, case 1), (220, 221), (8, case 27; 222, 223, 224), (154, case 23), (18), (25, case 1; 157, case 9; 158, case 9), (73, case 1; 157, case 7; 158, case 7), (73, case 2; 157, case 8; 158, case 8), (157, case 4; 83, case 1, 158, case 4), (157, case 5; 83, case 3; 158, case 5), (225), (226), (227, case 3), (228, case 1), (228, case 3), (228, case 4), (229, 230), (231), (68), (232, case 1), (232, case 2), (233), (234), (235), (236, case 1), (237, 132, case 1; 198, case 20), (37), (238), (239, case 7; 240, case 6), (241), (242), (243, 132, case 2), (244, case 1), (244, case 2), (244, case 3), (188, case 1), (188, case 3), (83, case 2), (245), (246), (247, 132, case 3; 109, case 14; 110, case 13), (248), (191, case 1), (249), (85, case 2; 86, case 14), (86, case 1; 112, case 2), (86, case 2; 112, case 3), (86, case 3; 112, case 4), (86, case 5; 112, case 5), (86, case 6), (86, case 7), (86, case 8), (86, case 9), (86, case 12), (86, case 15), (250), (251, 252), (253), (254, case 5), (255, case 2; 256, case 2; 257, case 2), (255, case 3; 256, case 3; 257, case 3), (132, case 8), (132, case 9; 196, case 1; 197, case 2; 109, case 10; 198, case 1; 110, case 11; 111, case 1), (132, case 10; 258, case 1; 197, case 4; 109, case 12; 198, case 5; 110, case 12; 111, case 2), (9, case 1), (259, case 2), (98, case 1), (260, case 3), (260, case 4), (261, 262, case 1 ?), (99, 112, case 7), (104, case 1), (4, case 2), (104, case 3), (263), (264), (265), (266), (267, case 3; 258, case 6; 197, case 7; 109, case 13; 198, case 7; 111, case 9; 111, case 4), (267, case 5; 258, case 9; 197, case 198, case 9), (268), (269, case 1), (270), (107), (197, case 6; 109, case 4; 198, case 6; 110, case 5; 111, case 3), (197, case 8; 271, case 10; 109, case 6; 198, case 10; 110, case 7; 111, case 5), (197, case 12; 271, case 13; 109, case 9; 198, case 14; 110, case 14; 111, case 6), (197, case 14; 271, case 11; 109, case 7; 198, case 12; 110, case 8; 111, case 7), (109, case 11; 198, case 21; 111, case 12), (272), (112, case 8), (198, case 18; 110, case 2; 111, case 13), (273), (274), (275), (276, case 1), (276, case 2), (276, case 3), (127, case 1), (127, case 3), (127, case 5), (127, case 6), (127, case 9), (127, case 10), (277, case 1), (277, case 2), (277, case 3), (278), (279), (240, case 7), (280, case 1), (100, case 1), (100, case 4), (100, case 5), (281), (282, case 1), (101), (125, case 1), (125, case 4), (125, case 6), (125, case 8), (125, case 9), (23, case 1), (23, case 2), (23, case 3), (23, case 4), (23, case 5), (23, case 9), (23, case 11), (283), (284), (285, case 1), (286, case 1), (286, case 2), (287, case 3), (287, case 4), (288, case 1), (288, case 2), (289, case 2; 290, case 2), (291), (292, case 2), (293), (114, case 6), (114, case 7), (115, case 7), (294, case 9), (295, case 1), (295, case 2), (296), (297), (298), (present report, case 2), (present report, case 3).

### Group C. Suggestive Cases Lacking One or More of the Cardinal Clinical Findings; Some with Pathological Findings

The 180 cases included in this group are those reported as follows: (299, case 4), (52), (53), (54, case 1), (49), (17, Obs. XII; 133, Obs. XII), (47, 227, case 2), (300, case 1), (301, case 1; 302), (303, 304, 305), (306, 307), (308), (309, 310) (311, case 2; 35), (72), (312, case 10), (154, case 25), (8, case 2), (8, case 3), (31), (75, case 1), (313), (314, case 2), (76, case 1), (157, case 3; 158, case 3), (315, case 2), (315, case 19), (144, case 2), (144, case 3), (26), (66), (227, case 1), (228, case 5), (316), (317, case 2), (82, case 1), (82, case 2), (82, case 3), (318, 319), (84, case 4), (320), (321, case 3a), (96, case 2), (322), (323, 324, case 1), (178, case 2), (325), (324, case 2), (324, case 3), (324, case 4), (326), (236, case 3), (184, case 2), (184, case 3), (38), (327), (83, case 4), (97), (120), (328), (329), (330), (27, case 1), (191, case 2; 260, case 2), (331, case 4; 132, case 4), (331, case 5; 132, case 5), (331, case 6; 132, case 6), (331, case 8), (332), (333), (40, case 3), (86, case 10), (86, case 11), (86, case 13), (103), (334), (335), (255, case 1; 256, case 1; 257, case 1), (28, case 2), (336), (132, case 7), (132, case 12; 197, case 1; 198, case 2), (337), (98, case 2), (98, case 3), (338), (260, case 1), (339), (90, case 3), (91), (340, 122), (267, case 1), (267, case 2; 197, case 9), (341), (43, 342), (258, case 5; 197, case 5; 198, case 4), (343, case 1), (343, case 2), (44), (197, case 13; 271, case 12; 109, case 8; 198, case 13; 110, case 10; 111, case 8), (344), (345), (109, case 3; 198, case 19; 110, case 4; 111, case 9), (109, case 5; 198, case 23; 110, case 6; 111, case 14), (112, case 6), (346, case 1), (346, case 12; 347, case 3), (348), (198, case 8), (198, case 16), (198, case 24; 111, case 15), (276, case 4), (127, case 2), (127, case 4), (127, case 7), (127, case 8), (349), (277, case 4), (350, case 3), (350, case 4), (350, case 5), (351, case 2), (351, case 1; 352, case 1), (352, case 2), (352, case 3), (240, case 9), (205, case 2), (353, case 1), (353, case 2), (100, case 2), (280, case 2), (29, case 2), (23, case 6), (23, case 7), (23, case 8), (23, case 10), (23, case 12), (23, case 13), (102, case 1), (102, case 2), (287, case 5; 290), (287, case 8), (354, discussion) (95, case 1), (95, case 2), (95, case 6), (95, case 10), (46), (289, case 1), (289, case 4; 290, case 4), (289, case 7), (355), (113), (356), (298, case 2), (357, case 1), (357, case 2), (357, case 3), (51), (292, case 1), (292, case 3), (292, case 5), (358), (359, case 1), (114, case 4; 115, case 2), (360), (361, case 12), (361, case 28), (361, case 31), (361, case 34), (361, case 35), (362), (363), (364, case 29), (115, case 3), (115, case 4), (365), (present report, case 4), (case 5), (case 6).

### Group D. Cases in Which the Diagnosis Seems Doubtful

The 43 cases in this group are those reported as follows: (48), (55), (62), (366), (50), (32), (314, case 1), (367), (368), (369), (370), (82, case 4), (371, case 5), (236, case 2), (372), (331, case 7), (373), (374), (375), (376), (267, case 4), (108), (94, case 1), (197, case 11; 198, case 11), (197, case 15), (377, case 2), (346, case 3), (346, case 4), (346, case 8), (347, case 4), (352, case 4), (378), (240, case 8), (353, case 3), (29, case 1), (29, case 3), (125, case 5), (125, case 7), (287, case 6), (95, case 3), (289, case 8), (292, case 4), (379).

### Group E Cases Showing Destructive Lesions of the Pituitary Body, but without the Typical Clinical Findings

The following 15 cases are included in this group (380, case 2), (299, case 3), (381), (382), (70), (383, case 6), (384), (385), (118), (172, case 2), (145, case 1), (386, case 12), (387, case 1), (387, case 9), (183, case 3)

### Group F Typical Clinical Cases, but with Normal Pituitaries

There are 14 reported cases in this category (388), (24), (155, case 2), (150, case 2), (151, case 2), (152, case 2), (389), (390), (78, 79, 11), (80), (391), (105, 106), (392), (130), (393), (present report, case 7)

### Group G Cases Reported without Sufficient Data for Classification

There are 84 cases reported that could not be classified because of insufficient data (394), (299, case 1), (299, case 2), (57, case 2), (395), (396, case 1), (397, case 6), (397, case 7), (397, case 8), (398), (74, case 16), (74, case 17), (25, case 6), (399), (163, case 2), (400, case 1), (400, case 2), (401), (402), (315, case 4), (315, case 28), (403, case 4), (67), (404, case 1, 405, case 2), (404, case 2, 405, case 6), (404, case 3, 405, case 8), (405, case 1), (405, case 3), (405, case 4), (405, case 5), (405, case 7), (405, case 9), (405, case 10), (405, case 11), (405, case 12), (405, case 13), (405, case 14), (405, case 15), (324, case 5, 406, case 1), (407),<sup>\*</sup> (85, case 3), (86, case A, 88), (40, case 1), (40, case 2), (408), (41, case 2), (42, case 4), (81), (409), (410), (94, case 2), (112, case 1), (112, case 9), (112, case 10), (100, case 3), (262, case 2), (111, case 16), (111, case 17), (111, case 18), (111, case 19), (111, case 20), (111, case 21), (111, case 22), (111, case 23), (111, case 24), (111, case 25), (111, case 26), (111, case 27), (111, case 28), (111, case 29), (111, case 30), (111, case 31), (111, case 32), (287, case 7), (95, case 4), (95, case 5), (95, case 7), (95, case 8), (95, case 9), (95, case 11), (95, case 12), (95, case 13), (95, case 14), (411)

### Group H Typical Cases of Anorexia Nervosa

For purposes of comparison, 20 cases of anorexia nervosa are referred to (125, case 3, 126, case 2), (412, case 1), (412, case 2), (412, case 3), (412, case 4), (412, case 5), (412, case 6), (412, case 7), (412, case 8), (413, case 1), (413, case 2), (414, case 1), (129, case 1), (129, case 2), (129, case 3), (129, case 4), (129, case 5), (129, case 6), (present report (case 8), (case 9)

In order to warrant inclusion in group A or group B, the four cardinal characteristics of Simmonds' disease had to be found in the data on a given case. These characteristics are a), loss of weight, b), loss of sexual function, c), asthenia, and d), a very low basal metabolic rate (below -20%). Since the earlier cases

were reported before basal metabolic rate determinations were customary, we have included them in groups A and B if they were typical clinically, furthermore, a few of the later cases in which basal metabolic rates were not reported have been admitted because in all other respects they were apparently characteristic

A few typical cases of anorexia nervosa have been listed and analyzed in order to emphasize the striking similarity of symptoms, physical stigmata and laboratory abnormalities. This parallelism has been noted also by others, for example, by Greene (127) and Richardson (128, 129) and its recognition is essential to any sound understanding of the problems involved in differential diagnosis because the two conditions may be alike in almost every detail, even in death. The final proof of the presence of Simmonds' disease rests on discovery of a destructive lesion of the adenohypophysis at autopsy. However, this criterion makes it difficult to account for the classical clinical picture (despite voracious appetite) in the patient described by Osgood (130), in whom a normal hypophysis was found at autopsy.

It is our intention to review in a subsequent paper the actual pathological lesions of the hypophysis reported in cases of true Simmonds' disease. The final paper in this series will be devoted to an analysis of the various therapeutic procedures which have been utilized, together with an appraisal of the results.

For obvious reasons, groups D, E, F and G have been excluded from the statistical analysis which follows. It would jeopardize the value of the statistics to include data from the dubious cases of group D, similarly, the cases in group E were not characteristic clinically although pathological pituitaries were found. To avoid controversy, we omitted the cases which were typical clinically but in which the pituitary body was normal. The question at once arises whether or not derangements of endocrine function are to be excluded purely because the pathologist can detect no cytological alterations. It has long been recognized that in unquestionable diabetes mellitus little or no change may be detected in the islets of Langerhans. Chemical hormonal changes may conceivably be operative in the absence of cellular abnormalities demonstrable by present methods of staining. Group G, in which the data are fragmentary, was automatically debarred. Although these cases were rejected from the statistical studies, they appear in this paper in order to complete the bibliography of Simmonds' disease.

Since variation in clinical findings is common to all diseases, our prerequisites for inclusion in group A may be too strict. Some of the cases in group C or even in group E, particularly those in which destructive lesions of the pituitary have been found,

\* We have been unable to find any record of this case except in Oppenheimer's discussion of the paper of Farquharson and Graham (182). The remark that the case showed most of the findings reviewed by Doctor Graham leads us to believe that it probably belongs in Group B, but we cannot include it because of inadequate data.



TABLE 1. SEX DISTRIBUTION

| Group   | Number of cases             | Female       | Male        | Ratio female: male |
|---|-----------------------------|--------------|-------------|--------------------|
| A (typical clinically, pathologically verified)     | 101<br>(sex not given in 1) | 65<br>(64%)  | 35<br>(35%) | 7:4                |
| B (typical clinically, no pathologic investigation) | 158                         | 128<br>(81%) | 30<br>(19%) | 4:1                |
| C (suggestive cases)                                | 180<br>(sex not given in 9) | 131<br>(73%) | 49<br>(22%) | 3:1                |
| H (cases of anorexia nervosa)                       | 20                          | 18<br>(90%)  | 2<br>(10%)  | 9:1                |

cases of true Simmonds' disease. However, we believe that even by these stringent standards a certain percentage of the cases in group B actually may be instances of anorexia nervosa. Richardson (129) has so designated several of them.<sup>9</sup> Therefore, for purposes of comparison, we have considered it desirable and more accurate to apply the same clinical standards to group A and group B.

#### STATISTICAL ANALYSIS OF CERTAIN SPECIAL FEATURES Anamnesis

**Sex distribution.** (Table 1). It is apparent at once that females predominate in all of the groups. The fact that in females anorexia nervosa is far more prev-

TABLE 2. AGE DISTRIBUTION

| Group                               | Years |       |       |       |       |       |       |       |
|-------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
|                                     | 0-9   | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 |
| A (101 typical, verified cases)     | 1     | 8     | 20    | 14    | 22    | 22    | 12    |       |
| B (158 typical cases, not verified) | 2     | 56    | 47    | 26    | 13    | 9     | 3     |       |
| C (180 suggestive cases)            | 2     | 19    | 44    | 48    | 34    | 22    | 4     | 1     |
| H (20 cases of anorexia nervosa)    |       | 11    | 7     | 2     |       |       |       |       |

<sup>9</sup> Sheldon (131) insisted that "large numbers of cases (of anorexia nervosa) were described, and are still being described, in all good faith as instances of Simmonds' disease. In fact, there are over 80 instances of this mis-reporting and approximately half of the published cases of anorexia nervosa are indexed under other names." An "industrious example" (of authors who make this error) was Kylin, who "in 1935 wrote a monograph on Simmonds' disease (132) which will always be one of the more important papers on anorexia nervosa."

alent (9:1) than verified Simmonds' disease (7:4) seems significant. Therefore the greater frequency of occurrence in females of the unverified group B suggests that some of these cases may actually have been instances of anorexia nervosa, even though they appeared clinically typical of Simmonds' disease.

**Age** (Table 2). Irrespective of what group is considered, true Simmonds' disease, or what may have been mistaken for Simmonds' disease, occurs but rarely before 10 years or after 65 years of age. It is therefore primarily a disease of adult life.

It is pertinent to observe that about half of the cases in which autopsies were made were reported prior to 1930, while less than 20 per cent of those in which no autopsies were reported were published before that time. These observations must be taken into account in appraising the age incidence in the two groups.

Most of the patients in the verified group were

TABLE 3. WEIGHT LOSS

| Group                               | Cases with weight loss mentioned | Cases with note of amount lost | Amount of actual weight loss |                   |                    |
|-------------------------------------|----------------------------------|--------------------------------|------------------------------|-------------------|--------------------|
|                                     |                                  |                                | Maximum                      | Minimum           | Average            |
| A (101 typical, verified cases)     | 63 (62%)                         | 42 (42%)                       | 51 kg<br>(112 lb)            | 3 5 kg<br>(8 lb)  | 20 4 kg<br>(45 lb) |
| B (158 typical cases, not verified) | 139 (90%)                        | 104 (66%)                      | 48 7 kg<br>(106 lb)          | 4 5 kg<br>(10 lb) | 19 3 kg<br>(42 lb) |
| C (180 suggestive cases)            | 109 (61%)                        | 83 (46%)                       | 75 5 kg<br>(166 lb)          | 1 4 kg<br>(3 lb)  | 16 9 kg<br>(37 lb) |
| H (20 cases of anorexia nervosa)    | 14 (70%)                         | 13 (65%)                       | 37 7 kg<br>(83 lb)           | 7 3 kg<br>(16 lb) | 19 5 kg<br>(43 lb) |

first seen when they were between the ages of 20 and 60 years, the mean age being 41. The corresponding figures for group B show predominance between the ages of 10 and 40 years with a mean age of 27. All of the instances of anorexia nervosa mentioned in this paper occurred between 13 and 35 years of age. Again, age grouping raises the suspicion that some of the cases in group B were instances of anorexia nervosa rather than of true Simmonds' disease.

**Weight loss** (Table 3). In at least 61 per cent of the cases in groups A, B, C, and H, loss of weight was specifically mentioned. However, it must have occurred more frequently in the verified group because cachexia was specifically mentioned in 65 per cent of the case reports. All of the patients included in groups A and B had some indication of weight-loss or cachexia.

The average amount of loss of weight was about the same in groups A, B, and H, namely approximately 20 kg. (44 lb.). The less typical cases of group C showed a slightly smaller average loss. Upon further analysis of the comparative weight-loss of males and females (which does not appear in the table), no appreciable difference was noted. The severest loss of weight suffered by any patient in group A, B, or C

was over 106 lb, with the highest figure (166 lb) in group C. In comparison, the greatest loss in the admittedly psychotic group did not exceed 83 lb.

**Asthma (Table 4)** This symptom was conspicuous in all groups, but was particularly striking in the patients who eventually died (group A, 90%). It was shared equally by both sexes. The high percentage of incidence in the verified cases would seem to require inclusion of this symptom as one of the characteristic features of the disease, however its frequent occurrence in other maladies, notably in Addison's disease, and the fact that it may develop late in the course of true Simmonds' disease diminish its value in differential diagnosis.

Asthma may be considered an inevitable consequence of marked loss of weight, but Meyer (95) has pointed out that this is not always true. It is well

TABLE 4 FREQUENCY OF ASTHMA

| Group                             | Males    | Females  | Total     |
|-----------------------------------|----------|----------|-----------|
| A (101 typical, verified cases)   | 33 (94%) | 57 (88%) | 91 (90%)  |
| B (158 typical cases, unverified) | 25 (83%) | 87 (68%) | 112 (71%) |
| C (180 suggestive cases)          | 27 (68%) | 92 (70%) | 122 (68%) |
| H (30 cases of anorexia nervosa)  | 1 (50%)  | 10 (56%) | 11 (55%)  |

known that many thin, wiry, healthy individuals exhibit the antithesis of asthenia, namely exceptional energy and endurance.

**Amenorrhea (Table 5)** The patients excluded in the second column of table 5 were under 11 years of age when first seen or had passed the menopause before the onset of the disease. Patients whose menstruation was scanty or irregular were not included in the third column, however, such symptoms should not be dismissed without clinical appraisal. A few females were included who were 15 years of age or over but had never menstruated.

A review of table 5 forces the conclusion that amenorrhea of longer or shorter duration is an outstanding phenomenon in groups A, B, and H, and a lesser but by no means negligible one in group C (64%). Anticipating a later analysis of the duration of symptoms, we merely note here that amenorrhea is an early symptom of either Simmonds' disease or anorexia nervosa.<sup>10</sup> Interestingly enough, Cushing and Davidoff stressed the fact that amenorrhea is one of the earliest symptoms in female acromegals, and

TABLE 5 FREQUENCY OF AMENORRHEA

| Group (Females)                   | Cases omitted because of age | Cases in which amenorrhea was specifically mentioned |
|-----------------------------------|------------------------------|--|
| A (65 typical, verified cases)    | 10 (15%)                     | 45 (82%)   |
| B (128 typical cases, unverified) | 8 (6%)                       | 117 (98%)  |
| C (131 suggestive cases)          | 4 (3%)                       | 81 (64%)   |
| H (16 cases of anorexia nervosa)  | 0                            | 18 (100%)  |

acromegaly is a pituitary endocrinopathy which is considered by some to be the opposite of Simmonds' disease.

**Loss of libido and potency (Table 6)** Here again, a certain number of males who were either too old or too young for the manifestation of this symptom was deducted from the totals.

Loss of libido and potency was a complaint in over half of the male patients, irrespective of whether they were classified in group A, B or C. This symptom may be ascribed to a deficiency of the anterior pituitary gonadotropic hormone rather than to malnutrition, since conspicuous vascularity has often been noted in advanced tuberculosis. Statistics were not computed in females since they rarely volunteer such a complaint and often no inquiry is made regarding it.

**Psychic changes** A close parallel is observed in the incidence of psychic disturbances in groups A, B and C (64, 55 and 49% respectively). The presence, therefore, of mental emotional abnormalities does not necessarily favor the diagnosis of anorexia nervosa. Symptoms most frequently noted are apathy, dullness, drowsiness,<sup>11</sup> confusion or disorientation, and depression. Curiously enough, the more serious psychopathic phenomena are encountered in true Simmonds' disease.

It may be argued that these psychopathic phenomena are not traceable directly to diminished pituitary

TABLE 6 FREQUENCY OF LOSS OF LIBIDO AND POTENCY

| Group (males)                      | Male cases in which specific mention was made |
|------------------------------------|---|
| A (35 typical, verified cases)     | 19 (59%)                                      |
| B (30 typical cases, not verified) | 20 (72%)                                      |
| C (40 suggestive cases)            | 21 (57%)                                      |
| H (2 cases of anorexia nervosa)    | 0   |

<sup>10</sup> Nicolle (415), in attempting to differentiate Simmonds' disease and anorexia nervosa stated that amenorrhea is usually a late event in Simmonds' disease, but according to the data compiled here this is not true.

<sup>11</sup> Pennetti (172) has noted somnolence in hypopituitarism and suggested a relation to hibernation in animals. May and Robert (340) believe that crises of somnolence point to disturbance of the nervous centers at the base of the brain.

tary function but are better interpreted as the natural consequences of weakness, cachexia, and profound metabolic disturbances. Weiner (206), stated that hypoglycemia and avitaminosis may be responsible for the mental symptoms. Nonetheless, that some of the patients with verified Simmonds' disease have been confined in institutions for the mentally abnormal is stressed here because of the difficulty noted in differentiating anorexia nervosa from true Simmonds' disease, a difficulty that is not diminished by encountering outspoken psychic disturbances in the verified cases. Nicolle (415), however, in 1939 attempted to differentiate the psychic manifestations of the two conditions by describing weakness, lethargy and somnolence as more characteristic of Simmonds' disease in contrast to the morbid energy and obstinacy exhibited by patients suffering from anorexia nervosa.

*Anorexia.* As is to be expected, the symptom anorexia, is far more striking in anorexia nervosa than in the verified cases of Simmonds' disease. It is mentioned more than twice as frequently in the former cases. However, loss of appetite does not exclude true Simmonds' disease.

The above items constitute the characteristics encountered in the anamnesis which we have considered of sufficiently outstanding interest to warrant inclusion in the published tables. The following items collated from careful reading of the case protocols are less crucial but are nonetheless interesting.

*Possible inciting factors.* In 13 of the 101 cases (13%) in which the diagnosis of Simmonds' disease was verified at autopsy, the onset of the disease seemed to follow or coincide with an infectious process not associated with pregnancy. No particular type of infection predominated, but a wide variety has been listed, including meningitis, 'pulmonary infections,' influenza, malaria and tularemia. In 17 (11%) of the 158 cases in group B, which were typical clinically but not verified, the disease began with an infection. In this group the occurrence of syphilis, osteomyelitis, rheumatic fever, catarrhal jaundice, diphtheria, dysentery and encephalitis was also mentioned. In the suggestive group C, 13 of the 180 cases (7%) included an infection associated with onset of the disease. In only one of the cases of anorexia nervosa listed here did the onset coincide with an infection. Although infectious disease is not a frequent cause of pituitary cachexia, a serious infection immediately preceding the onset would lead to the assumption that true pituitary pathology exists.

Of much greater significance from the etiological standpoint is the part played by pregnancy. Pregnancy occurred just prior to the onset of the disease

in 27 of the 67 verified female cases (42%). In over half of these (14 of 27 cases) abnormal hemorrhage at the time of delivery was specifically alluded to in the case report. In this connection it is pertinent to call attention to the observations of Sheehan (386, 416, 124) and Sheehan and Murdoch (287, 289, 290). From clinical and pathologic studies they concluded that the pituitary undergoes a rapid involution at the time of the puerperium. They assumed that a sudden reduction of blood flow to the gland takes place and that, if this is complicated by a circulatory collapse due to hemorrhage, the blood flow may be reduced almost to nothing. Thrombosis may thereby be precipitated in the sinuses of the gland with consequent infarction and necrosis. In 8 of the 27 cases (30%) sepsis occurred, with and without hemorrhage at delivery. However, Sheehan believed that the pituitary damage in such circumstances takes place before sepsis has had time to develop and is more likely due to hemorrhage and collapse.<sup>12</sup>

In 17 of the 128 females in group B (13%) pregnancy was considered the inciting factor. Twelve of these were associated with hemorrhage and in 4 sepsis was mentioned. The figures for group C were as follows: parturition as a possible cause of onset was

<sup>12</sup> Effkemann and Müller-Jäger (417) were able to follow up the cases of 84 women who had lost 800 to 1600 cc. of blood at parturition. Their cases were painstakingly tabulated with special emphasis on symptoms and were then separated into 3 groups according to the amount of blood lost. These statistics seemed to indicate that among the 20 patients who had lost between 1200 and 1600 cc. of blood, 60% showed diminished menstrual function and 50% remained sterile. However, 40% of the 20 patients became obese, whereas only 10% became thin. These observations are reminiscent of what happens in women following the menopause: most of them show a tendency to gain weight while the minority tends to shrivel. The causes of these phenomena are not known.

Although there is no experimental proof that the pituitary is indispensable to life (indeed, there is evidence to the contrary), under certain conditions acute pituitary inadequacy may be responsible for rapid collapse and death. Naturally, under such circumstances there is insufficient time for the development of Simmonds' disease. For example, Brown and Eder (418) reported the case of a 43-year-old primipara who had hypertension and albuminuria and was delivered by forceps after 16 hours of labor. The placenta was retained and expressed later. The patient suffered severe collapse with only moderate loss of blood. Despite stimulants and two blood transfusions the temperature rose to 104° F., the systolic blood pressure dropped from 184 to 60 and the patient died 4 days later. At autopsy the adrenals and ovaries were normal. The pituitary weighed 1 gm. and the anterior lobe stained poorly (necrobiosis) and contained areas of frank necrosis resembling infarction. Gotshalk and Tilden (419) reported a similar case.

Another example of acute infarction of the pituitary followed by death within 24 hours was reported by Kotte and Vonderahe (420) under the title, "The Houssay phenomenon in man." Their patient had had diabetes mellitus for 5 years and in the 2 months prior to death signs of tuberculosis had developed. He was brought into the hospital in a semi-stuporous state with a temperature of 102.8° F. Four+ glycosuria had been noted the day before, but 24 hours later no sugar was found in the urine; the blood sugar was 31 mg. % and later below 20 mg. %, also in the spinal fluid. Autopsy disclosed an infarction involving almost the entire anterior lobe of the pituitary.

noted in 40 of the 131 female cases (31%) Hemorrhage was reported in 23 of these 40 cases (58%) and sepsis in 6 (15%) In none of the 20 cases of anorexia nervosa assembled for comparison was any mention made of parturition as an inciting factor, in fact, the majority of the patients were young unmarried females

One may conclude, therefore, that when either parturition or a severe acute infection is followed by progressive loss of weight with asthenia, amenorrhea and a low basal metabolic rate, true pituitary damage exists.<sup>13</sup> Admittedly, in a large number of these cases no such clue to onset can be elicited and the origin of the disease remains a mystery. However, there are likewise no adequate explanations for the origin of many other endocrinopathies, such as the onset of acute diabetes mellitus in childhood without appar-

TABLE 7 DURATION

| Group                            | Cases in which data were given | No. cases of duration |        |         |            | Length of Time |        |       |
|----------------------------------|--------------------------------|-----------------------|--------|---------|------------|----------------|--------|-------|
|                                  |                                | 1 yr or less          | 2-5 yr | 6-10 yr | Over 10 yr | Max yr         | Min mo | Av yr |
| A (101 typical verified cases)   | 90 (89%)                       | 20                    | 28     | 19      | 23         | 44             | 1      | 7.9   |
| B (158 typical cases unverified) | 128 (81%)                      | 48                    | 60     | 17      | 9          | 30             | 2      | 3.1   |
| C (180 suggestive cases)         | 141 (78%)                      | 44                    | 54     | 23      | 20         | 40             | 2 days | 5.2   |
| H (10 cases of anorexia nervosa) | 20 (100%)                      | 6                     | 12     | 2       | 0          | 8              | 5      | 2.78  |

ent inciting cause. A familial incidence was noted only in the case of Zondek (25, 157)

In the cases reported by Cyran (395), Rouvillois, Reverchon et al (309, 310), and Reinhardt (398), the onset of the disease apparently followed a head injury. Also Homer Rush (295), in a personal communication, described a typical case in which the onset followed fracture of the skull. One of our patients whose case is reported for the first time in this paper (case 4 in Case Summaries) developed a suggestive clinical picture following a head injury which caused an internal carotid aneurism. Tying off the carotid on the affected side resulted in some amelioration of symptoms.

**Duration** Table 7 has been compiled in order to determine how long definite symptoms had been present before the patient consulted the author of the report. In gathering these statistics, the various items were recorded separately for each sex, but as there

<sup>13</sup> Nicolle (415) contended that the onset of Simmonds' disease is abrupt in contrast to the gradual appearance of the symptomatology in anorexia nervosa. This may be true when Simmonds' disease develops rather promptly after a severe infection or consequent to hemorrhage at parturition, but the distinction does not hold, for example, when the pathological cause is a pituitary tumor.

TABLE 8 PREGNANCY BEFORE ONSET OF THE DISEASE

| Group (Females)                  | Cases with previous pregnancies | Number of previous pregnancies |                |        |
|----------------------------------|---------------------------------|--------------------------------|----------------|--------|
|                                  |                                 | 1                              | 2-5            | Over 5 |
| A (65 typical, verified cases)   | 30 (46%)                        | 3                              | no of cases 15 | 12     |
| B (128 typical cases unverified) | 18 (14%)                        | 4                              | 11             | 3      |
| C (131 suggestive cases)         | 42 (32%)                        | 10                             | 23             | 9      |
| H (18 cases of anorexia nervosa) | 1 (6%)                          | 0                              | 1              | 0      |

were no noteworthy differences in duration in males and females, these more detailed figures were omitted.

The following points seem to deserve comment. In groups A, B, and C the symptoms may exist for a long time, the maximum being 44, 30 and 40 years respectively. Accordingly, even though the condition ends fatally, it may run a long course. In the verified group the duration of symptoms prior to consulting the author averaged 7.9 years, while in the unverified group the average was 3.1 years. In this connection it should be noted that 46 per cent of the cases in which autopsies were performed were reported prior to 1930 while less than 16 per cent of the cases without records of autopsies appeared before that time. This finding may imply that a more widespread acquaintance with the disease has resulted in its earlier recognition. The course may be swift or may extend over many years. Apparently the duration of the disease depends upon the type of underlying lesion, as for instance a malignant tumor, and perhaps especially upon the degree of secondary adrenal incapacity.

**Pregnancy before and after onset of disease** (Table 8). Of the 65 females in group A, 30 (46%) had one or more pregnancies prior to the onset of the disease. Indeed, 12 of these 30 were pregnant over 5 times and occasional reports of 9 and 11 pregnancies were found. As might be expected, pregnancy rarely occurs after the onset of the disease. In the typical verified cases of group A, pregnancy occurred in only one instance after onset (164, case 1, 165, case 2, 166). However, Sheehan (386, 416, 124) and Sheehan and Murdoch (289, 290) have recorded several cases in which the clinical picture was relatively mild and a subsequent pregnancy with its concomitant anterior pituitary hyperplasia had a decidedly favorable effect (autotherapy) (287, case 5, 289, cases 1, 2, 4, 7, 8, 290, cases 2, 4, 386, case 12).

**Cold intolerance** Forty one of the 101 patients in group A (41%) complained of intolerance to cold weather. Fifty two of the 158 patients in group B

(33%) and 27 per cent of the patients in group C made the same complaint. However, in only 3 of the 20 cases of anorexia nervosa was this symptom recorded.

This symptom could be interpreted, in association with the profoundly low basal metabolic rate, as a

Table 9 presents in considerable detail a number of diseases that have been reported in association with Simmonds' disease. These may or may not have had any relation to the onset or course of Simmonds' disease, but because of their frequent occurrence they are recorded here. In addition, a number of miscel-

TABLE 9. ASSOCIATED DISEASES AND MISCELLANEOUS SYMPTOMS

| Disease or Symptom                             | Group A<br>(101 typical verified cases) |         |         | Group B<br>(158 typical cases, not verified) |         |         | Group C<br>(180 suggestive cases) |         |         | Group H<br>(20 cases of anorexia nervosa) |         |         |
|--|---|---------|---------|--|---------|---------|-----------------------------------|---------|---------|---|---------|---------|
|  | Male                                    | Female  | Total   | Male   | Female  | Total   | Male                              | Female  | Total   | Male                                      | Female  | Total   |
| Tuberculosis (active or quiescent)             | 7(20%)                                  | 11(17%) | 18(18%) | 2(7%)  | 3(2%)   | 5(3%)   | 2(5%)                             | 4(3%)   | 6(3%)   | 0   | 0       | 0       |
| Syphilis (clinical, serological or in history) | 5(14%)                                  | 8(12%)  | 14(14%) | 0  | 5(4%)   | 5(3%)   | 3(7%)                             | 6(5%)   | 9(5%)   | 0   | 0       | 0       |
| Diabetes Mellitus                              | 0                                       | 1(2%)   | 1(1%)   | 0  | 0       | 0       | 0                                 | 1(1%)   | 1(1%)   | 0   | 0       | 0       |
| Diabetes Insipidus                             | 8(23%)                                  | 7(11%)  | 15(15%) | 6(20%)                                       | 9(7%)   | 15(10%) | 11(28%)                           | 6(5%)   | 17(9%)  | 0   | 1(6%)   | 1(5%)   |
| Oliguria                                       | 2(6%)                                   | 4(6%)   | 6(6%)   | 1(3%)  | 6(5%)   | 7(4%)   | 1(2%)                             | 8(6%)   | 9(5%)   | 0   | 0       | 0       |
| Edema, including                               | 6(17%)                                  | 12(18%) | 18(18%) | 2(7%)  | 14(10%) | 16(10%) | 3(7%)                             | 11(8%)  | 14(8%)  | 0   | 4(22%)  | 4(20%)  |
| Ascites and                                    | 2                                       | 1       | 3       | 0  | 1       | 1       | 0                                 | 2       | 2       | 0   | 1       | 1       |
| Pleural Fluid                                  | 2                                       | 1       | 3       | 0  | 0       | 0       | 0                                 | 0       | 0       | 0   | 0       | 0       |
| Gastrointestinal                               | 20(57%)                                 | 35(54%) | 55(54%) | 16(53%)                                      | 82(64%) | 98(62%) | 12(30%)                           | 70(53%) | 83(46%) | 1(50%)                                    | 12(67%) | 13(65%) |
| Symptoms excluding anorexia, including         |   |         |         |  |         |         |                                   |         |         |   |         |         |
| indigestion                                    | 1                                       | 1       | 2       | 1  | 15      | 16      | 0                                 | 0       | 0       | 1   | 4       | 5       |
| pain   | 5                                       | 9       | 14      | 1  | 13      | 14      | 3                                 | 23      | 26      | 0   | 1       | 1       |
| cramps   | 0                                       | 1       | 1       | 0  | 3       | 3       | 0                                 | 4       | 4       | 0   | 0       | 0       |
| nausea   | 4                                       | 3       | 7       | 4  | 5       | 9       | 3                                 | 6       | 9       | 1   | 0       | 1       |
| vomiting                                       | 13                                      | 20      | 33      | 8  | 22      | 30      | 8                                 | 24      | 32      | 0   | 4       | 4       |
| diarrhea                                       | 3                                       | 5       | 8       | 1  | 4       | 5       | 3                                 | 6       | 9       | 0   | 0       | 0       |
| constipation                                   | 6                                       | 19      | 25      | 7  | 49      | 56      | 1                                 | 32      | 34      | 0   | 6       | 6       |
| Voracious Appetite                             | 0                                       | 1(2%)   | 1(1%)   | 0  | 2(2%)   | 2(1%)   | 0                                 | 1(1%)   | 1(1%)   | 0   | 0       | 0       |
| Headache                                       | 15(43%)                                 | 16(25%) | 31(31%) | 10(33%)                                      | 26(20%) | 36(23%) | 11(28%)                           | 33(25%) | 44(24%) | 0   | 1(6%)   | 1(5%)   |
| Vertigo and / or Fainting                      | 6(17%)                                  | 11(17%) | 17(17%) | 4(13%)                                       | 16(12%) | 20(13%) | 7(17%)                            | 30(23%) | 37(21%) | 0   | 1(6%)   | 1(5%)   |
| Epilepsy or Convulsions                        | 2(6%)                                   | 6(9%)   | 8(8%)   | 1(3%)  | 2(2%)   | 3(2%)   | 0                                 | 1(1%)   | 1(1%)   | 0   | 0       | 0       |
| Youthful Appearance                            | 2(6%)                                   | 0       | 2(2%)   | 0  | 3(2%)   | 3(2%)   | 2(5%)                             | 5(4%)   | 7(4%)   | 0   | 0       | 0       |

secondary hypothyroid phenomenon, but it should also be recalled that adrenalectomized animals and patients with Addison's disease are extremely sensitive to low temperatures. The secondary deficiency of adrenal cortical function which undoubtedly occurs in Simmonds' disease should be considered as a possible factor. Patients with anorexia nervosa supposedly do not have thyroid or adrenal deficiency, yet they occasionally suffer from cold intolerance, though less frequently than the patients in the other groups. Upon further statistical analysis it was found that patients with cold-intolerance did not disclose on the average lower basal metabolic rates, blood pressures, hemoglobin levels or red blood cell counts than the average figures for the entire groups.

Associated diseases and miscellaneous symptoms.

laneous symptoms are recorded which did not appear sufficiently important to be included in the extensive tables of case reports.

Tuberculosis is of such common occurrence that one would expect to encounter it now and again even in as rare a malady as Simmonds' disease. However, that it should have been noted as either quiescent or active in 18 per cent of the verified cases is somewhat surprising. In a few of these it occurred in the pituitary body itself. The discrepancy between this incidence of 18 per cent and the minimal occurrence of tuberculosis in groups B and C as well as its complete absence in the 19 cases of anorexia nervosa is noteworthy. One might deduce from these findings that malnutrition alone does not render a patient more vulnerable to tuberculosis. This conclusion is borne out

by the extreme rarity of tuberculosis as a complication of hyperthyroidism, a disease in which weight loss is conspicuous

The incidence of syphilis does not vary markedly in groups A, B and C. Here again actual gumma of the hypophysis has been reported in a few cases as the outstanding pathological finding. The blood serum in 46 cases in group A, 42 cases in group B and 41 cases in group C, was tested for syphilis by the Wassermann, Kahn or Hinton reaction. The positive tests in these instances were 15 per cent in group A, 14 per cent in group B and 12 per cent in group C. The spinal fluid Wassermann was positive in 2 of 18 cases in group A, in 1 of 10 cases in group B and in 1 of 14 cases in group C. Therefore, syphilis of the central nervous system, as evidenced by positive spinal fluid tests, may be considered a negligible factor in all three groups. The role of syphilis as a causative factor in Simmonds' disease is not impressive.<sup>14</sup>

The incidence of diabetes insipidus in groups A, B and C, namely 15, 10 and 9 per cent respectively, cannot be ignored since this disease itself is rare. The important investigations of Ranson and co-workers suggest that a lesion in the neural pathway from the supraoptic nucleus to the posterior pituitary, or a deficient production of the pars intermedia-posterior lobe antidiuretic hormone must be held responsible. Probably this complication would occur even more frequently if the pathologic alterations causing Simmonds' disease did not involve principally the anterior pituitary.

Apparently the water balance in Simmonds' disease can be upset in either direction, for oliguria has been noted occasionally.

The occurrence of edema in group A is noteworthy, though it was reported less frequently in groups B and C. A study of the correlated findings seems to exclude its cardiac or renal origin in most of the cases. Perhaps the explanation is similar to that for hunger edema with lowered blood proteins which was suggested by Brugseh in discussing the paper of Zondek (1936). Accumulation of fluid in the body cavities (ascites and pericardial or pleural effusion) may be merely an internal manifestation of this same condition. Incidentally, these complications have been discovered occasionally in myxedema as reported by Mussio Fournier (421), Hertzler (422), Evans (423), ourselves (424), and Hansen (425).

Even when anorexia is excluded, the various gastrointestinal symptoms occur with about equal frequency in all four groups, namely 54, 62, 46 and 65 per cent respectively. Further details are shown in

table 9. There is nothing characteristic about these symptoms, however, that would help in differential diagnosis. Evidently they are associated with malnutrition and asthenia of psychic, pituitary or adrenal origin. On the whole, they are by no means as conspicuous as in Addison's disease.

#### PHYSICAL FINDINGS

*Cachexia or emaciation.* The outstanding symptom, emaciation, inspired the descriptive designation, 'hypophyseal cachexia'. Analysis of the reports shows that it was a striking characteristic in 65 per cent of the cases in the verified group, in 58 per cent of the cases typical clinically, and in 75 per cent of the cases recognized as anorexia nervosa. In group C, in which the diagnosis of Simmonds' disease was suggestive but some of the cardinal characteristics were absent, cachexia occurred in only 25 per cent of the cases. This observation increases the doubt as to the correctness of the diagnosis of Simmonds' disease in many of the cases in group C. Although the postmortem findings in several of them were quite characteristic. It is reasonable to assume that this disease, like most others, may occur in varying degrees of severity and may at times display only a partial clinical picture. The incidence of cachexia was statistically analyzed according to sex and no noteworthy difference was found in any of the groups. A striking atrophy of the tissue of the buttocks was noted in several of the cases in our series in which the emaciation was advanced.

A careful study of 40 undernourished persons was published by Kerppola in 1939 (361). He found that one half of his group showed an increased glucose tolerance, relative lymphocytosis and low gastric acidity, one third showed a slightly small sella turcica, slight anemia and granulocytopenia, one-fourth of 35 females had menstrual disturbances, one-eighth of the group had basal metabolic rates of -20% or under (we have included these 5 cases in group C). Kerppola concluded that only 5 of these 40 thin persons showed evidence of 'pituitary weakness'. As remarked before, this study raises the question as to whether there may not be a mild form of Simmonds' disease.

*Amount underweight.* (Table 10) The amount under ideal weight could be calculated only when the patient's age, sex, height, and weight were given in the case report. The resulting calculations give a fairly accurate demonstration of the degree of undernutrition. The most extreme instance was reported by Mertz (178, case 1), a verified case of Simmonds' disease in a male who was 47.5 kg (104 lb) underweight.

*Premature senility.* (See table 11 for classification of

<sup>14</sup> A case somewhat suggestive of Simmonds' disease but in which a normal BMR was found was reported by Falta in 1925 (76).

TABLE 10. AMOUNT UNDERWEIGHT FROM NORMAL STANDARDS

| Group                               | Cases in which calculation was possible | Amount Underweight    |                     |                      |
|-------------------------------------|---|-----------------------|---------------------|----------------------|
|                                     |   | Maximum               | Minimum             | Average              |
| A (101 typical, verified cases)     | 32 (32%)                                | 47.5 kg.<br>(104 lb.) | 6.1 kg.<br>(13 lb.) | 21.2 kg.<br>(47 lb.) |
| B (158 typical cases, not verified) | 97 (61%)                                | 36.5 kg.<br>(80 lb.)  | 0                   | 20.7 kg.<br>(46 lb.) |
| C (180 suggestive cases)            | 73 (41%)                                | 37.6 kg.<br>(83 lb.)  | 1 kg.<br>(2 lb.)    | 17.2 kg.<br>(38 lb.) |
| H (20 cases of anorexia nervosa)    | 19 (95%)                                | 26.8 kg.<br>(59 lb.)  | 10 kg.<br>(22 lb.)  | 20.7 kg.<br>(46 lb.) |

cases in which definite mention of this symptom was made). Evidently premature ageing is more characteristic of organic disturbance, for it occurs in true Simmonds' disease with far greater frequency, especially in the male, than it does in the functional psychosis of anorexia nervosa. Thomson (355) has included striking photographs of premature senility in a recent case report.

*Loss or absence of axillary and/or pubic hair.* (See table 12 for classification of cases in which definite mention of these symptoms was made.) Again, this striking phenomenon is far more likely to occur in true Simmonds' disease than in anorexia nervosa. It is probably due to the deficient secretion of the anterior pituitary gonadotropic hormone which results in secondary gonadal insufficiency. No doubt 'exceptions prove the rule'; but it must be noted that such loss of sexual hair has been reported in anorexia nervosa, and contrariwise, overabundant body hair has been reported in cases of verified Simmonds' disease, as in a case personally observed by the authors (125, case 2; 126, case 1). Herrick (22) and Nicolle (415) insisted that loss of body hair is an important diagnostic sign.

Naturally, uncomplicated cases of alopecia totalis cause no confusion in differential diagnosis. However, axillary and pubic hair may be lost in cases of hemochromatosis with cirrhosis of the liver and spleen and in cases of secondary atrophy of the thyroid, adrenals

TABLE 11. FREQUENCY OF PREMATURE SENILITY

| Group                               | Male | Female | Total |
|-------------------------------------|------|--------|-------|
| A (101 typical, verified cases)     | 46%  | 45%    | 45%   |
| B (158 typical cases, not verified) | 47%  | 26%    | 30%   |
| C (180 suggestive cases)            | 12%  | 10%    | 10%   |
| H (20 cases of anorexia nervosa)    | 0    | 6%     | 5%    |

TABLE 12. LOSS OR ABSENCE OF AXILLARY AND / OR PUBIC HAIR

| Group                               | Males | Females | Total |
|-------------------------------------|-------|---------|-------|
| A (101 typical, verified cases)     | 80%   | 82%     | 80%   |
| B (158 typical cases, not verified) | 77%   | 53%     | 58%   |
| C (180 suggestive cases)            | 43%   | 60%     | 53%   |
| H (20 cases of anorexia nervosa)    | 0     | 17%     | 15%   |

and gonads (426). Althausen and Kerr (427, 428) have called attention to the secondary sexual hypoplasia in cases of hemochromatosis. Their patients (all males) showed thinning of the beard so that shaving was required less frequently, together with loss of hair from the axillae and chest and thinning of the pubic escutcheon so that it resembled the female type.

Sheldon (131), like many others, agreed that anorexia nervosa and the physical changes caused by famine may simulate the 'clinical tableau' of Simmonds' disease. In attempting to differentiate between the functional and organic diseases, he stated that "an increased growth of hair has never been described in any of the case reports of Simmonds' disease, whereas it is frequent in anorexia nervosa" and has been reported as a result of widespread famine. Furthermore, he stated that hypertrichosis has a "teleological significance—to assist in preserving the body heat." Though this hypothesis is most intriguing, we must again point out that one of our own patients in whom the diagnosis was verified by autopsy (125, case 2; 126, case 1) displayed an overabundance of downy body hair.

*Genital atrophy or infantilism.* (See table 13 for classification of cases in which definite mention of these symptoms was made.) This truly objective finding occurs with about equal frequency in all groups. It is no doubt associated, as part of the same process consequent to gonadal deficiency, with amenorrhea, loss of libido and potency, loss of sexual hair, and premature senility. Its apparently greater frequency in males is probably explained by external obviousness. However, absence of atrophy does not necessarily

TABLE 13. GENITAL ATROPHY OR INFANTILISM

| Group                               | Male | Female | Total |
|-------------------------------------|------|--------|-------|
| A (101 typical, verified cases)     | 60%  | 42%    | 49%   |
| B (158 typical cases, not verified) | 60%  | 23%    | 34%   |
| C (180 suggestive cases)            | 38%  | 39%    | 37%   |
| H (20 cases of anorexia nervosa)    | 0    | 44%    | 40%   |

preclude deficient function. Furthermore, even a severe degree of genital atrophy (and more or less loss of sexual hair and premature senility) may occur as a result of almost any wasting disease. For example, Bauer (429) reported these findings in a case of chronic sprue, but he ascribed them to a secondary pituitary deficiency and commented on the resemblance of the clinical picture in his case to Simmonds' disease. A striking discrepancy was, however, an elevated basal metabolic rate.

**Blood pressure.** Study of table 14 reveals that some of the patients in groups A, B and C had mild hypertension. On the other hand, some patients in all three groups had severe hypotension, almost as low as in grave cases of Addison's disease. However, the average systolic blood pressure in these groups was not conspicuously different from that occasionally found in normal or slightly asthenic individuals.<sup>15</sup>

A detailed statistical analysis reveals that a systolic pressure under 90 mm. Hg was found in 38 per cent of the cases in group A, in 44 per cent of the cases in

TABLE 14 BLOOD PRESSURE

| Group                               |           | Cases in which data were given | Max | Min | Av |
|-------------------------------------|-----------|--------------------------------|-----|-----|----|
| Values in mm. Hg                    |           |                                |     |     |    |
| A (101 typical, verified cases)     | Systolic  | 68 (67%)                       | 160 | 50  | 96 |
|                                     | Diastolic | 47 (47%)                       | 100 | 40  | 62 |
| B (158 typical cases, not verified) | Systolic  | 121 (77%)                      | 142 | 60  | 91 |
|                                     | Diastolic | 98 (62%)                       | 100 | 0   | 61 |
| C (180 suggestive cases)            | Systolic  | 131 (73%)                      | 160 | 55  | 98 |
|                                     | Diastolic | 100 (56%)                      | 110 | 0   | 65 |
| H (20 cases of anorexia nervosa)    | Systolic  | 20 (100%)                      | 108 | 72  | 89 |
|                                     | Diastolic | 20 (100%)                      | 82  | 40  | 59 |

group B, in 27 per cent of the cases in group C and in 50 per cent of the cases in group H. In summary one is forced to conclude that the hypotension in these cases is concomitant merely with the malnutrition, and is not nearly as marked as in Addison's disease.

Additional interesting physical findings not considered of sufficient importance to be included in the tables are given below.

**Interference with growth (height).** The height of 42 adults in group A was recorded. Only one of these was under 4 feet, 10 inches. In group B, 8 out of 99 adults, and in group C 9 of 88 adults were below this height. It seems reasonable to assume that in these patients the anterior pituitary deficiency began in childhood and therefore a degree of dwarfism resulted. But, as mentioned in the discussion of

TABLE 15 FREQUENCY OF OCCURRENCE OF DRY SKIN, LOSS OF NON-SEXUAL HAIR, DECAY OR LOSS OF TEETH

| Group                               | Dry Skin | Loss of Hair of Eyebrows, Scalp, Beard | Decay or Loss of Teeth |
|-------------------------------------|----------|--|------------------------|
| A (101 typical, verified cases)     | 55 (54%) | 51 (50%)                               | 42 (42%)               |
| B (158 typical cases, not verified) | 81 (51%) | 56 (35%)                               | 33 (21%)               |
| C (180 suggestive cases)            | 67 (37%) | 70 (39%)                               | 34 (19%)               |
| H (20 cases of anorexia nervosa)    | 5 (25%)  | 1 (5%)                                 | 2 (10%)                |

age, true Simmonds' disease is a disease of adult life and only occasionally arises before puberty. Therefore dwarfism is a rare phenomenon. The anterior pituitary deficiency of childhood, 'hypophysial infantilism,' which is characterized by retardation of growth and sexual infantilism without adiposity, is by no means uncommon and never proceeds to a fatal termination unless caused by a tumor. Oddly enough, 2 girls aged 15 and 16 years respectively, who were considered as having anorexia nervosa, were less than 4 feet, 8 inches in height.

**Dry skin.** Loss of non-sexual hair. Decay or loss of teeth (See table 15 for classification of cases in which specific mention of these symptoms was made.) Dryness of the skin is attributable either to secondary hypothyroidism or to inanition. Loss of nonsexual hair, dental caries and occasional loss of teeth are probably of trophic origin, yet it is a curious circumstance that these changes have rarely been reported in anorexia nervosa in which malnutrition is equally pronounced.<sup>16</sup>

**Pulse.** In 9 of the 42 cases (21%) of group A in which the pulse rate was mentioned, a definite bradycardia of 60 beats per minute or less was noted. The same was observed in 25 of 60 cases in group B (42%), and in 5 of 16 cases (31%) in group H. For some reason bradycardia of this degree was exceptional in group C (8% of 47 cases). The slow pulse rate may be related to the lowered basal metabolic rate, but since the latter is so consistently low, it is surprising that bradycardia does not occur more frequently. May, in discussing a paper on 'anorexia mentale' by Mollaret and Peron (430), stated that bradycardia did not occur in this condition and that its presence favored a diagnosis of Simmonds' disease. Our statistics do not bear out this observation (see section on differential diagnosis).

**Temperature.** A markedly subnormal temperature (35.5°C or 96°F or under) was noted in 13 of 37 cases (35%) of group A, in 8 of 57 cases (14%) of group B, in 4 of 29 cases (14%) of group C, and in 2 of 15 cases (13%) of group H. This obvious discrepancy forces one to assume that marked hypothermia in a patient who has cachexia, asthenia, loss of sexual function and a lowered basal metabolism, suggests the diagnosis of Simmonds' dis-

<sup>15</sup> Schellong (324, 323, 406) has emphasized that the drop in blood pressure with change of posture and also following exercise is marked in Simmonds' disease. However, since this tendency to postural hypotension may occur in other states, including malnutrition, it is hardly specific for Simmonds' disease.

<sup>16</sup> Nicolle (415) stated that loss of body hair and loss of teeth have never been seen in anorexia nervosa. Use of the word never seems an exaggeration.



case rather than that of anorexia nervosa. Here also, it is somewhat surprising that a low temperature is not encountered more frequently, especially in groups A and B in which the basal metabolic rates are consistently low.

**Pigmentation** In less than one-third of the verified cases (24%) some degree of pigmentation, varying in intensity from yellow to brown, was mentioned. It was less frequent in the other groups. This pigmentation may be

TABLE 16 BASAL METABOLIC RATE

| Group                               | Cases in which data were given | Max. | Min. | Av.  |
|-------------------------------------|--------------------------------|------|------|------|
| A (101 typical, verified cases)     | 41 (41%)                       | -17% | -51% | -33% |
| B (156 typical cases, not verified) | 121 (72%)                      | -20% | -67% | -35% |
| C (180 suggestive cases)            | 110 (61%)                      | +40% | -52% | -18% |
| H (20 cases of anorexia nervosa)    | 20 (100%)                      | -14% | -51% | -29% |

ascribed to adrenal involvement (in view of the pronounced pigmentation seen in Addison's disease) and perhaps the same explanation may be given for its occurrence in many cases of outright myxedema. However, that the characteristic pigmentation of Addison's disease is due directly to suprarenal deficiency has never been proved. On the contrary, it does not vanish, as a rule, upon administration of either the cortical or medullary adrenal hormone. Zondek's finding of a pigmentary factor in the pars intermedia which acts on the melanophores of the skin is intriguing in this connection, but it seems premature to ascribe the pigmentation occasionally seen in Simmonds' disease directly to the hypophysis. Berkman (431), in describing the clinical findings in 117 cases of anorexia nervosa, mentioned that brownish discoloration of the skin was noted in 12 cases.

**Pallor** was mentioned in 48 per cent of the cases in group A, in 23 per cent of the cases in group B, and in 23 per cent of the cases in group C. In the cases of anorexia nervosa no pallor was noted.

**Gout** was exceedingly rare in all groups. This is not surprising inasmuch as secondary atrophy rather than overgrowth of the thyroid would be expected.

**Atrophy of the breasts.** Probably the general body emaciation so overshadowed the condition of the mammary glands that their atrophy was accepted as part of the tissue-wasting process. Yet mammary atrophy, as distinguished from mere loss of fat in the breast, would be expected as part of the loss of sexual function. It was mentioned specifically in only 23 per cent of the 65 females in group A, in 8 per cent of the 128 females in group B, in 11 per cent of the 131 females in group C, and in only one instance in the 18 cases of thin women diagnosed as anorexia nervosa.

## Laboratory Findings

**Basal metabolic rate.** From the perusal of table 16 it is obvious that a markedly low basal metabolic rate characterizes both the verified and the unverified cases of Simmonds' disease as well as those frankly recognized as anorexia nervosa. The lowest levels reached in groups A, B and H (-51%, -67%, and -51%) are quite as low as those encountered in severe myxedema. One is tempted to postulate that a deficiency of the thyrotropic fraction from the anterior pituitary is responsible for the low rate, but against such an assumption is the failure to affect clinical improvement in the majority of these patients by the administration of thyroid substance in either true Simmonds' disease or anorexia nervosa. More likely, then, is the conception that the lowered metabolism is a result of malnutrition.

**Fasting blood sugar.** (Table 17). In addition to the foregoing data, further analysis discloses that in 43 per cent of the 42 cases in group A a fasting blood sugar of 60 mg. % or under was reported whereas only 14 per cent of the 96 cases in group B, 7 per cent of the 83 cases in group C, and 21 per cent of the 14 cases in group H showed comparably low values. The presence of fasting hypoglycemia, together with the four cardinal characteristics (emaciation, asthenia, low basal metabolic rate and loss of sexual function), is therefore suggestive of true Simmonds' disease.

TABLE 17 FASTING BLOOD SUGAR

| Group                             | Cases in which data were given | Max | Min | Av |
|-----------------------------------|--------------------------------|-----|-----|----|
| Values in mg %                    |                                |     |     |    |
| A (101 typical, verified cases)   | 42 (42%)                       | 114 | 24  | 66 |
| B (158 typical cases, unverified) | 96 (61%)                       | 138 | 36  | 79 |
| C (180 suggestive cases)          | 83 (46%)                       | 153 | 35  | 82 |
| H (20 cases of anorexia nervosa)  | 14 (70%)                       | 134 | 26  | 73 |

**Glucose tolerance tests.** Glucose tolerance tests were reported in 21 of the 101 verified cases (21%). Of these 8 were interpreted as normal, 2 as diabetic in type and 11, or 65 per cent, as 'flat' (showing increased tolerance).

In group B, glucose tolerance tests were reported in 59 of 158 cases (37%). Of these 17 were interpreted as normal, 11 were considered to show mild or frank diabetic tendencies and 21 showed the opposite state of increased tolerance as exemplified by a flat curve.

Ten others at some point during the test reached a definitely hypoglycemic level. In other words, normality, diabetic tendency, increased tolerance, and an occasional hypoglycemic level were fairly evenly distributed.

Glucose tolerance tests were reported in 47 of the 180 suggestive cases (26%). A study of these tests showed a spread similar to that found in the previous group.

In 12 of the 20 cases of anorexia nervosa (60%) glucose tolerance tests were recorded. In 6 cases of the 12 (50%) the tolerance for glucose was increased. However, this number may be too small to have any significance.

Sensitivity to insulin was rarely mentioned (group A, 7%, group B, 8%, group C, 4%, and group H, 0%). Hypoglycemic coma occurred in 5 per cent of the verified cases and only once in group C, it was not mentioned in groups B and H. In view of the Houssay and Biasotti experiments on dogs (432) and the likely

concept that deficient anterior pituitary function leads to hypoglycemia rather than hyperglycemia and it is borne out further by the fact that definite hypoglycemic coma was reported in 4 cases.<sup>17</sup>

In addition to these data, which constitute the laboratory investigations listed in the tables, other interesting information collected from the 615 case protocols is appended hereto.

TABLE 19 GASTRIC ACIDITY

| Group                            | Cases in which data are given | Achylia | Achlorhydria | Low free acid | Normal Normal | Hyper acidity |
|----------------------------------|-------------------------------|---------|--------------|---------------|---------------|---------------|
| A (101 typical verified cases)   | 20 (20%)                      | 3       | 7            | 7             | 2             | 1             |
| B (158 typical cases unverified) | 38 (24%)                      | 5       | 11           | 5             | 14            | 3             |
| C (180 suggestive cases)         | 33 (18%)                      | 6       | 6            | 7             | 12            | 2             |
| H (20 cases of anorexia nervosa) | 2 (10%)                       | 0       | 1            | 0             | 1             | 0             |

TABLE 18 HEMOGLOBIN, RED BLOOD CELL COUNTS, EOSINOPHILES

|  | Group A (101 typical, verified cases) | Group B (158 typical cases, unverified) | Group C (180 suggestive cases) | Group H (20 cases (20 cases nervosa) |
|--|---------------------------------------|---|--------------------------------|--------------------------------------|
| Hemoglobin Cases in which data were given      | 57 (56%)                              | 68 (43%)                                | 71 (39%)                       | 10 (50%)                             |
| Values   |                                       |   |                                |                                      |
| Maximum  | 102%                                  | 103%                                    | 110%                           | 105%                                 |
| Minimum  | 40%                                   | 31%                                     | 21%                            | 52%                                  |
| Average  | 65%                                   | 76%                                     | 74%                            | 82%                                  |
| Red Blood Cells Cases in which data were given | 59 (58%)                              | 73 (46%)                                | 74 (41%)                       | 9 (45%)                              |
| Values/cu mm                                   |                                       |   |                                |                                      |
| Maximum  | 5,600,000                             | 5,800,000                               | 5,600,000                      | 5,190,000                            |
| Minimum  | 2,000,000                             | 1,500,000                               | 730,000                        | 3,000,000                            |
| Average  | 3,710,000                             | 3,980,000                               | 3,800,000                      | 4,150,000                            |
| Eosinophiles Cases in which data were given    | 41 (41%)                              | 46 (29%)                                | 59 (33%)                       | 9 (45%)                              |
| Values   |                                       |   |                                |                                      |
| Maximum  | 40%                                   | 12%                                     | 30%                            | 2%                                   |
| Minimum  | 0                                     | 0                                       | 0                              | 0                                    |
| Average  | 6.3%                                  | 2.6%                                    | 4.1%                           | 0.6%                                 |

hood that a contra-insular or diabetogenic hormone is elaborated in the anterior pituitary, it is interesting to note that frank diabetes mellitus has been reported in but one case of verified Simmonds' disease. Theoretically this observation would harmonize with the

Hemoglobin, red blood cells and eosinophiles (Table 18). Even though severe anemia is not characteristic of verified Simmonds' disease, the degree of anemia in group A was greater than that in groups B, C and especially H.<sup>18</sup>

It is interesting to note that the average percentage of eosinophiles is definitely above the normal level in group

<sup>17</sup> In this connection we call attention to the case reported by Anna Pettersson (77) under the designation 'Hypoglycemia'. The patient was a woman aged 33, 26 lb. underweight, with a systolic blood pressure of 90 mm Hg. She had been amenorrheic for 6 years following her last pregnancy which had been complicated by hemorrhage (Sheehan (386, 416, 124) and Sheehan and Murdoch (287, 289, 290) have noted pituitary damage in several instances in which death followed hemorrhage at parturition). Pettersson's patient was first seen in hypoglycemic shock with a blood sugar of 25 mg %. It was noted that she had lost considerable body hair as well as several teeth and that her nails were brittle and her skin was dry. At autopsy the pituitary was described as 'small' (no microscopic report was given), the ovaries were atrophic and the islets of Langerhans were small. In his opinion this was probably a case

Kolleston (433) refers to Wilder (434) as having observed attacks of spontaneous hypoglycemia in Simmonds' disease, but a perusal of Wilder's paper reveals that his two patients were obese rather than cachectic and had menstruated normally. Certainly, they were not cases of Simmonds' disease. Wilder reported them as examples of a new syndrome, 'hypophyseal spontaneous hypoglycemia'.

In this connection certain experimental work is pertinent. Cori, Marks and White (435) reported insulin sensitivity following hypophysectomy in rabbits, and Mahoney (436) reported hypoglycemia following removal of the pituitary in dogs.

<sup>18</sup> Snapper, et al. (352) reported several patients who showed some of the characteristics of Simmonds' disease such as loss of weight and sexual hair, in whom achlorhydria and pronounced anemia and even combined system disease developed subsequently. They believed the pituitary was initially responsible for the subsequent course. Van Bogaert (285) presented 2 patients with similar neurological lesions but without hyperchromic anemia. The gastric acidity in one of these patients was normal. He called the condition 'pituitary pseudo tabes'.

A, whereas this is not the case in groups B and C, and emphatically not in group H. In 21 of the 41 cases (51%) in group A, eosinophilia of 5 per cent or over was noted, and in 9 of these the percentage was 10 to 40. It is difficult to appraise the significance of such an eosinophilia, especially since the same abnormality has been noted in the opposite pituitary state, acromegaly.

**Gastric acidity.** (Table 19). In about one-fifth of the verified cases gastric acidity was determined, and in 85 per cent of these either achylia, achlorhydria or low free acid was found. The same phenomenon was noted in

and 55 per cent of those in group H. All roentgenograms in group H were considered normal. However, in 18 of the 42 cases in group A (43%), in 21 of the 96 cases in group B (22%) and in 18 of the 75 cases in group C (24%) enlargement, destruction, or calcification of the sella was evident. This finding would lead to the suspicion that a tumor,<sup>21</sup> a cyst or a chronic infectious process is the underlying pathologic lesion in these cases. Such a condition, therefore, in an emaciated asthenic patient who has lost sexual function and has a low metabolic rate would be strong evidence in favor of true Simmonds' disease.

TABLE 20. COURSE OF DISEASE AND RESPONSE TO TREATMENT

| Group                             | Number of patients |            |                   |                             |          |               |                        |
|-----------------------------------|--------------------|------------|-------------------|-----------------------------|----------|---------------|------------------------|
|                                   | Dead               | Unimproved | Slightly improved | Temporarily rarely improved | Improved | Much improved | Spontaneously improved |
| A (101 typical, verified cases)   | 98 (97%)           | 28 (28%)   | 4 (4%)            | 20 (20%)                    | 5 (5%)   | 1 (1%)        | 0                      |
| B (158 typical cases, unverified) | 8 (5%)             | 16 (10%)   | 19 (12%)          | 9 (6%)                      | 75 (47%) | 21 (13%)      | 3 (2%)                 |
| C (180 suggestive cases)          | 36 (20%)           | 15 (8%)    | 23 (13%)          | 8 (4%)                      | 59 (33%) | 18 (10%)      | 2 (1%)                 |
| H (20 cases of anorexia nervosa)  | 1 (5%)             | 3 (15%)    | 0                 | 0                           | 9 (45%)  | 8 (40%)       | 0                      |

groups B and C, but in only 55 and 58 per cent respectively. Comment is withheld regarding group H since gastric acidity was determined in only 2 of the 20 cases. However, Berkman (431) in reporting the clinical findings in 117 case of anorexia nervosa mentioned achlorhydria in 11 cases and a tendency to hypoacidity in the group as a whole. As has been stated, Snapper et al. (352) have advanced the interesting idea that achylia may result from dysfunction of the anterior pituitary and that it may lead to pernicious anemia or even to combined system disease.

**Plasma cholesterol.** Although no sweeping conclusions can be drawn from the small number of cases in which the plasma cholesterol was determined, it is nonetheless interesting that the average level was slightly above normal in groups A and C, namely 234 mg.% and 238 mg.% respectively. The highest level attained was in a verified female case, namely 560 mg.%. No comparison can be made with anorexia nervosa as the plasma cholesterol was determined in only one case. A high blood cholesterol may be attributed to secondary hypothyroidism.

**Other laboratory findings.** The rather scanty data on nitrogen partition (non-protein nitrogen, blood urea nitrogen, uric acid, urea, creatinine, and blood proteins) disclosed no noteworthy abnormalities. A similar statement can be made concerning the fragmentary reports of blood sodium chloride,<sup>19</sup> chlorides, sodium, potassium, calcium, phosphorus and carbon dioxide combining power, as well as electrocardiograms.<sup>20</sup>

**Sella turcica.** Roentgenograms of the sella turcica were obtained in 42 per cent of the cases in group A, 61 per cent of those in group B, 42 per cent of those in group C

## COURSE

**Reaction to treatment.** (Table 20). Naturally, the outlook for the effectiveness of any therapeutic endeavors would be most unfavorable if the verdict depended on the results of treatment in the 101 patients of group A, since nearly all of them died.<sup>22</sup> The duration of life may have been prolonged somewhat in a few of these patients by glandular therapy, but in many of them it was of no help whatever. Many varieties of pituitary preparations of the whole gland or of the anterior lobe only were tried, both orally and hypodermically. Thyroid substance, thyroxin, adrenal, ovarian and testicular extracts, gonadotropins and insulin were used. Whereas these hormones almost never prevented a fatal outcome in the group of 101 verified cases, they produced astounding improvement in 60% of comparable cases in group B.

The argument may be advanced that Simmonds' disease may vary in severity, that possibly a fortunately potent batch of gland extract may have been available or that the dosage may have been large and the treatment more persistent in some of the cases in which favorable responses were noted. However,

<sup>21</sup> Horrax (22) stated that symptoms of Simmonds' disease are frequently noted in neurosurgical clinics and interpreted as due to the pressure of pituitary adenomata; following removal of the adenomata marked improvement may occur. A patient of DeMartel and Guillaume (206) showed marked improvement after surgical drainage of a 'cholesteatomatous pseudo-cyst' of the pituitary.

<sup>22</sup> In the cases of group A, in all of which pituitary destruction in some form was verified by autopsy or operation, failure to improve under treatment was not surprising in view of Smith's observation (22) that pituitary tissue never regenerates. This statement apparently did not take into account the hyperplasia of pregnancy, of castration or of the menopause.

<sup>19</sup> Meyer (95) reported a lowered sodium chloride in 5 out of 8 cases.

<sup>20</sup> Sheehan (124) stated that low voltage in the electrocardiogram is a frequent finding in Simmonds' disease.

close scrutiny shows no noteworthy difference in either the endocrine preparations used or the manner of their administration in the two groups. Therefore some of the improvement which undoubtedly took place may conceivably be ascribed to unintentional psychotherapy, to spontaneous resumption of pituitary activity or to coincidence. Yet, however conservative or skeptical one may be, a careful reading of many of the protocols forces one to believe that in some cases specific pituitary therapy must be given credit for the extraordinary improvement which occurred. The results with any one product were not consistent, but improvement from treatment occasionally seemed most convincing. In this connection one is reminded of the occasional benefits obtained by pancreatic therapy in the treatment of diabetes mellitus prior to the discovery of insulin.

However, failure to improve under treatment and even death do not establish a diagnosis of Simmonds' disease, as illustrated by the two striking cases published respectively by Richardson (129, case 3), and Osgood (130). Although they were typical of Simmonds' disease in symptomatology and in physical and laboratory findings, and the clinical courses ended in death, normal pituitary bodies were found at autopsy in both cases. Because of the normal pathological findings, Richardson considered his case as one of anorexia nervosa. Osgood called attention to the voracious appetite of his patient throughout most of the course of the disease. During a long period of hospitalization, she consumed 3000 calories daily although no diarrhea, fever or elevated basal metabolic rate which might account for her progressive emaciation occurred. This course would seem to exclude a diagnosis of anorexia nervosa, and the cause for the patient's emaciation and death remained a mystery.

Thus, again the question is raised whether severe disturbances of hormonal chemistry cannot occur in the absence of demonstrable histopathology. Bauer (429) inclined to such an interpretation as the explanation for Osgood's case, he believed that pituitary deficiency may exist without microscopic evidence. One does not hesitate to diagnose Cushing's disease or diabetes mellitus clinically, even though subsequent autopsy fails to reveal a lesion of the hypophysis, adrenals or islets of Langerhans.

#### ETIOLOGY, PATHOGENY, PATHOGENESIS

In 1910 Crowe, Cushing and Homans (437) reported the production of cachexia in puppies consequent to total (?) hypophysectomy. Emaciation developed within 3 weeks. In 1927 Smith (438) presented convincing experimental evidence that complete removal of the hypophysis in rats resulted in cachexia in the adults, in failure to grow in the young, in atrophy of the sex glands with loss of sexual func-

tion, in atrophy of the thyroid, parathyroid and adrenal cortex, in early senility, in general loss of tone and in splanchnomercia. These striking changes were noticeable 15 days after removal of the pituitary and reached their maximum 30 days after the operation. The damage could be rectified within a few days by daily pituitary transplants, thus growth was resumed and sexual function restored. Evans, Meyer, Pencharz and Simpson (439) were able to rectify the cachexia and to repair the adrenal damage of hypophysectomized rats by injections of their anterior-pituitary growth hormone. Houssay (440) found that hypophysectomy in dogs lowered the basal metabolic rate.

The status of these hypophysectomized animals simulates closely the clinical picture of Simmonds' disease. Deficiency of the growth stimulating hormone would account for cachexia and splanchnomercia, lack of the gonadotropic hormones would seem responsible for amenorrhea, frigidity, impotence, atrophy of the genitalia, loss of sexual hair, and premature senility, insufficiency of the adrenotropic fraction could produce secondary atrophy of the adrenal cortex with consequent asthenia, hypotension, hypoglycemia, occasional pigmentation, some of the gastro-intestinal symptoms, and probably the lethal outcome, lack of thyrotropic hormone may be responsible for low basal metabolic rate, cold intolerance, dryness of the skin, bradycardia and hypothermia, lastly, lack of the diabetogenic or contrainsular hormone could be a factor in causing hypoglycemia.

Although we regard these interpretations as satisfactory and in agreement with modern experimental investigations, for the sake of completeness mention is made here of other conceptions. In 1926 Urechia and Elekcs (315) questioned the pituitary origin of Simmonds' disease and stated that the primary seat of the disease was in the tuber cinereum. Accordingly they named the disease 'cachéxie tubérienne'.<sup>23</sup> Roussy and Mosinger (441) espoused a similar interpretation and stated definitely that cachectic states could result from lesions in the hypothalamus. The same conception was advocated by Mogilnitzky (174) and Marnesco and Parhon (187). Bailey and Bremer in 1922 (442) produced cachexia in two dogs and testicular degeneration in one of them by injury to the tuber cinereum, the pituitaries were later found to be normal microscopically.

<sup>23</sup> These authors noted that emaciation occasionally accompanies general paresis, catatonia, schizophrenia and tabes, and concluded therefore that severe weight loss might be of cerebral origin. They believed that the nodes in the tuber cinereum are sensitive to infections and intoxications and can control temperature and tissue metabolism, and that lesions of these nodes might cause emaciation. They presented microscopic sections from cases of diabetes and general paresis showing infiltration around these nodes and stated that in senile cachexia marked alterations occurred in the periventricular and supraoptic nuclei.

In recent years the interest in hypophyseal-hypothalamic interrelationships, which have been especially emphasized by Cushing (443), Fisher, Ingram and Ranson (444), and others, has increased. Kylin (132) suggested that a disturbance of any part of the 'pituitary-hypothalamus unit' might be responsible for Simmonds' disease. This reminds one of Biedl's hypothesis (referred to by Solis-Cohen and Weiss (445) as "seductive") that diabetes insipidus and dystrophia adiposogenitalis may be caused by: a), a lesion of the hypophysis producing deficient increments; b) a lesion obstructing the neural pathways to the hypothalamus and preventing the pituitary hormones from energizing the genito-trophic centers of the tuber cinereum; or c), normal secretion and normal pathways but disease of the hypothalamic centers which therefore would be unable to respond to the customary stimuli. This hypothesis straddles the pituitary stalk with one foot in the sella turcica and the other in the hypothalamus; it affords a platform broad enough for all parties to the controversy and seems almost too plausible to be true.

The conception of Falta (17, 133, 18, 19) as well as of Claude and Gougerot (14, 15, 16) that a simultaneous fibrosis involves several of the ductless glands seems untenable in the light of our present knowledge.

We have referred previously to perplexing cases, such as the one reported by Osgood (130), which were characteristic clinically but in which normal pituitaries were disclosed at autopsy. One is tempted to accept the suggestion of some writers that in these cases the pituitary is functionally rather than organically impaired and thus fails to stimulate the thyroid, sex and adrenal glands.

In many diseases, such as hyperthyroidism, adrenal cortical disease and Laurence-Moon-Biedl syndrome, the recognition of minor, abortive, atypical or partial 'formes frustes' has been considered proper, and such have also been described for Simmonds' disease. Zondek and Koehler (82) wrote of transient functional deficiency of the anterior lobe with moderate thinness. Von Bergmann (85) used the term, 'hypophyseal wasting (Magersucht)' to describe milder cases in which the pituitary might be intact but functionally deficient. He believed that the term, 'hypophyseal cachexia,' should be reserved for the fatal cases in which the pituitary was destroyed. Wahlberg (104) coined the eponym, 'asthenia gravis hypophyseogena,' for mild, reversible cases. Schüpbach (276) referred to a mild functional form of the disease which improved under therapy, and a similar conception was introduced by Mainzer (353) under the expression, 'minor endocrinology,' as distinct from fully developed clinical pictures. Hicks (262) called the milder cases 'anterior pituitary dystrophy.'

Although theoretically one must concede that such partial or functional forms of the disease may occur, examination will disclose that they are usually found in young unmarried girls and are more likely instances of anorexia nervosa. However, Sheldon (446, 131) suggested pituitary abnormality as a factor in anorexia nervosa. He wrote of a pituitary 'blackout' of psychological origin on a background of endocrine infantilism and termed this 'functional Simmonds' disease.' In his second paper he elaborated this hypothesis, and in emphasizing the almost exact parallelism clinically between true Simmonds' disease, anorexia nervosa and starvation, he hypothesized the existence of a similar central hypothalamic mechanism which inhibits anterior pituitary activity in all three conditions. The only differences he conceded were that in Simmonds' disease actual destruction of anterior pituitary cells takes place, in starvation an adjustment of the pituitary activity to a lowered level of existence occurs, and in anorexia nervosa a 'psychologic brake' is exerted on pituitary function. These ideas seem somewhat fanciful; and yet, we recognize the occurrence of acute exophthalmic goiter consequent to emotional shock, fright or grief, and of temporary suppression of the menses for similar reasons. Schur and Medvei (350) discussed the psychologic causation of endocrine dysfunction in 5 cases of anorexia nervosa.

The original conception of Gull that the disease known as anorexia nervosa arises from 'a morbid mental state' which manifests itself in a repulsion for food, has become traditional. As a result the other characteristics of the clinical picture develop. These include progressive loss of weight, weakness, amenorrhea and low basal metabolic rate. The amenorrhea is regarded as a more or less inevitable effect of starvation. In this connection one is reminded of the 'starvation amenorrhea' reported in central Europe during the war of 1914 to 1918. Sheldon (131) took issue with this conception, maintaining that "in between one-third and one-half of the cases" the amenorrhea "arises at either the same time as the anorexia or even before it, and cannot possibly be attributed to starvation." He introduced the term 'amenorrhea nervosa.'

It is equally disconcerting to account for the complete absence of any clinical evidence of deranged pituitary function in cases in which autopsy reveals destruction of the pituitary body. Several such cases are recorded in *group E*. Occasionally the neurosurgeon is called upon to remove a pituitary tumor in order to prevent blindness; and some of these patients exhibit no endocrine abnormalities. Why the same pathologic lesion produces glandular upheaval in one case and little or no sign of interference with

function in another remains a puzzle. Interesting in this connection is a strange case of Sheehan (386)—that of a woman who died during her twelfth pregnancy and in whom a shriveled, fibrotic pituitary was found at autopsy. Her extraordinary fertility and the lack of any evidence of Simmonds' disease are difficult to explain unless perhaps some aberrant hypophyseal tissue carried on normal pituitary function.<sup>24</sup>

Reference should be made here to six cases in group F (388, 155, 390, 78-79, 39, 393) in which the pituitaries were normal at autopsy but definite pathology was encountered in close proximity to the anterior lobe. Since all of these cases were typical clinically of Simmonds' disease, interference with the function of the adenohypophysis is conceivable although no cellular changes were found. Such a supposition seems tenable when one reflects on the intimate neural connections which link the hypophysis and hypothalamus (as previously discussed).

#### DIFFERENTIAL DIAGNOSIS

Since the outstanding characteristic of Simmonds' disease is marked loss of weight, one must first exclude the more customary causes of emaciation, such as tuberculosis,<sup>25</sup> severe hyperthyroidism, pellagra, sprue, and metastatic malignancy.<sup>26</sup> These conditions are readily differentiated as a lowered basal metabolic rate is not found in any of them. The natural shriveling of old age can hardly be confused with hypophyseal cachexia even though a subsequent autopsy may disclose visceromelia and generalized atrophy of the ductless glands including the pituitary (450).

Occasionally Addison's disease may present a problem in differential diagnosis as some of the patients with this primary adrenal disturbance are

considerably underweight. However, the characteristic bronze pigmentation of adrenal cortical insufficiency is rarely seen in Simmonds' disease. Although some pigmentation has been noted occasionally, the characteristic spotting of the mucous membranes has never been reported in primary pituitary disease. Gastrointestinal complaints are far more pronounced and hypotension is likely to be more severe in Addison's disease. As a rule the basal metabolic rate is not as low in primary adrenal disease, hypogonadism, notably genital atrophy and loss of sexual hair,<sup>27</sup> is far more striking in Simmonds' disease. Finally, patients suffering from Simmonds' disease only occasionally derive benefit from adrenal cortical extract or high salt intake. Stephens (115), by using the salt excretion test of Cutler, Power and Wilder, has made possible the recognition of cases in which such a regime is helpful. He observed laboratory evidence of adrenal cortical insufficiency in six of his seven cases of hypopituitarism. When in rare cases differential diagnosis remains doubtful, recourse may be had to the trial of such a salt poor regime for a few days, but only if the patient is under careful hospital supervision. A patient with Simmonds' disease is less likely to lapse into crisis under such conditions, the severity of the crisis depending upon the degree of secondary atrophy of the adrenal cortex.<sup>28</sup>

However, the truly difficult problem in differential diagnosis is the distinction between Simmonds' disease and anorexia nervosa. In addition to the reports already mentioned, this subject has been discussed recently by others (123, 413, 414, 415, 451-461). In spite of these contributions, the problem remains a difficult one. Therefore we have attempted to clarify it somewhat by statistical evaluation of the observations made in group A (verified typical Simmonds' disease) and those made in group H (anorexia nervosa). These comparisons follow. For the sake of clarity and emphasis they have been arranged in outline form.

<sup>24</sup> In this regard Melchionna and Moore (447) have recently recorded finding pituitary tissue in the pharynx in 51 of 54 consecutive autopsies at the New York Hospital.

<sup>25</sup> Heidkamp (448) reported the case of a boy aged 13 who died from widespread tuberculosis involving the cervical glands and the skin, with a cold abscess on the wall of the chest and pulmonary cavitation. Autopsy disclosed that a tuberculoma replaced the hypophysis. However, the emaciation seemed adequately accounted for by generalized tuberculosis especially as the other features of Simmonds' disease were absent. A similar case in a weak and emaciated 13 year-old girl was reported by E. Wagner (394). She had been scrofulous from her first year of life. Autopsy disclosed that her pituitary was largely replaced by tuberculous granulation tissue.

<sup>26</sup> In the older literature, syphilis especially when it involves the central nervous system, is mentioned as a cause of cachexia. However, modern therapy has practically eliminated this condition. As examples of cachexia resulting in part at least from vomiting consequent to increased intracranial pressure, two cases reported by Kollants (449) are cited. The two patients were females aged 17 and 28 (the latter sterile), who died as a result of primary sarcoma of the hypophysis. These two cases are not included in our tables because cachexia was the only symptom suggestive of Simmonds' disease.

<sup>27</sup> See case reported by Deusch (72), under the diagnosis, 'Ad dison's disease with pluriglandular insufficiency'.

<sup>28</sup> Aitken and Russell (336) reported the case of a waiter aged 50 years. The onset was acute and the patient was semiconscious for 3 days with a temperature of 105° F. The condition was explained subsequently by discovery of a sudden hemorrhage which had destroyed a chromophobe adenoma and practically the entire pituitary body. For the remaining 10 months of life the patient suffered from the effects of pituitary deficiency which in his case were: moderate wasting, great general weakness, a low systolic blood pressure of from 80 to 95 mm Hg, a low level of blood sugar (fasting, 67 mg % and not higher than 95 mg % following 100 gm glucose), and attacks of vomiting and prostration. These attacks and the hypotension, together with the marked asthenia, were suggestive of Addison's disease. At autopsy secondary atrophy of the suprarenals was found to be pronounced, there was, however, no Addisonian pigmentation. On the other hand, Ibbotson (369) reported a case in which the patient was deeply pigmented but improved clinically on oral pituitary therapy.

# REVIEW AND SUMMARY OF ANALYTICAL DATA FOR THE PURPOSE OF DISTINGUISHING BETWEEN SIMMONDS' DISEASE AND ANOREXIA NERVOSA

A striking similarity is noted in the incidence of three of the four cardinal characteristics:

1. *Cachexia*—65% and 75% respectively; *amount underweight*—average 21.2 and 20.7 kg. respectively; *amount of weight lost*—average 20.4 and 19.5 respectively.
2. *Loss of sexual function*—amenorrhea in 82% and 100% of the females respectively.
3. *Lowered basal metabolic rate*—average -33% and -29% respectively.
4. *Asthenia*. There is a definite difference in the frequency of occurrence of this symptom. It was noted in 90% of the cases in which Simmonds' disease was verified, but in only 55% of those recognized as cases of anorexia nervosa. However, this distinction is of doubtful differential value although it may be stated that the absence of asthenia in a young unmarried cachectic female would lead one to doubt the possibility of the diagnosis of Simmonds' disease.<sup>29</sup>

## Other Items of Similarity

1. *Gastrointestinal disturbances* (excluding the symptom anorexia)—54% and 65% respectively.
2. *Bradycardia*—incidence of 21% and 31% respectively.
3. *Edema*—in 18% and 20% respectively.
4. *Blood pressure*—averages, 96/62 and 89/59 mm. Hg respectively.

## Items Disclosing Significant Differences Between Simmonds' Disease and Anorexia Nervosa

1. *Onset post partum*. Onset soon after parturition, especially if delivery has been complicated by excessive hemorrhage and collapse, is strongly indicative of true Simmonds' disease. This inciting cause was never noted in the cases of anorexia nervosa but was recorded in 42% of the 65 verified female cases in group A.
2. *Onset following a severe infection*. This factor was mentioned only once in group H. However, it seems possible that a debilitating infection may predispose a neurotic individual to psychic anorexia.
3. *Alterations in the sella turcica*. Roentgen-ray evidence of a deformed sella turcica or calcification within it was noted in 43 per cent of the proved

cases of Simmonds' disease, whereas no abnormalities in or about the sella were found in the cases of anorexia nervosa. This finding, therefore, in correlation with supporting clinical evidence, strongly suggests the diagnosis of Simmonds' disease.

4. *Reaction to treatment*. Marked improvement in response to treatment casts doubt on the presence of Simmonds' disease. This statement holds for the past and the immediate present, but may require considerable modification when anterior pituitary hormones become available which are comparable in potency and specificity to thyroid, insulin, parathormone, cortin, estradiol, and testosterone. In group A (verified Simmonds' disease) in which the mortality was 97 per cent, only 6 per cent of the patients were considered 'improved' or 'much improved' by any form of treatment. However, in the anorexia nervosa group 85 per cent could be so classified. A marked improvement after psychotherapy or a spontaneous return to complete health would strongly suggest the diagnosis of anorexia nervosa.

5. *Loss or absence of axillary and pubic hair (sexual hair)*. This condition was far more common in verified Simmonds' disease than in anorexia nervosa—in 80 per cent as against 15 per cent.

6. *Premature senility*. This condition also may be considered as due to lack of gonadotropic hormone. It occurred far more frequently in the verified group than in group H (45% as against 5%).

7. *Atrophy of the breasts in females* occurred in 21 per cent of the cases in group A but not at all in group H.

8. *Pallor* was mentioned in 48 per cent of the cases in group A but not at all in group H. This difference is hard to explain as no marked differences were found in hemoglobin values or in red blood cell counts.

9. *Eosinophilia*—averages, 6.3% and 0.6% respectively.

## Summary of Other Points of Interest

1. *Psychic abnormalities and anorexia*. As would be expected, mental-emotional disturbances and the symptom anorexia occurred more commonly in group H, namely in 95 per cent as compared to 64 per cent and 39 per cent in group A. Although their presence favors the diagnosis of anorexia nervosa, it by no means excludes the diagnosis of Simmonds' disease.

2. *Sex*. Females predominate in both groups, but the proportion of females is much higher in group H (9:1<sup>30</sup> as against 7:4 in group A).

3. *Average age*. The patients with true Simmonds' disease fall for the most part into the older decades

<sup>29</sup> That this is not invariably true was proved by the experience with one of our patients in whom the diagnosis of Simmonds' disease was verified at autopsy. The patient was a 17-year-old unmarried emaciated girl who developed terminal asthenia but who had played tennis a short time before her last entry into the hospital.

<sup>30</sup> Ryle (462) personally observed 51 patients with anorexia nervosa of which 46 were females and 5 were males, a ratio of 9:1.



(average 41 years as against 21 years in group H)<sup>21</sup>

4 Duration of symptoms was greater in the cases of true Simmonds' disease (average 79 years as against 28 years in anorexia nervosa)

### Observations With Regard to Groups B and C

A survey of the statistical data for these groups (group B), cases typical clinically but without pathologic verification, group C, suggestive cases, some with pituitary pathology) reveals that the percentages of incidence of the various symptoms, signs and laboratory tests in general range between the extremes of group A and group H. This observation may be interpreted as suggesting that some of the cases in groups B and C are more likely to be instances of anorexia nervosa than of true Simmonds' disease. This is one of the reasons why only 20 cases of anorexia nervosa were selected for critical analysis, as we thought the number sufficient to indicate the general trend. Furthermore, comparison with the findings in Ryle's (462) group of 51 patients whom he observed personally, proves this to be the case.

### CONCLUSIONS

1 An exhaustive search of the literature, correspondence with colleagues, and our personal experience, have yielded 595 cases with more or less suggestive evidence of Simmonds' disease. These cases have been subdivided into 7 groups and are presented in tabular form. With a few exceptions, each case report had been read in the original publication.

2 In 101 cases the diagnosis of Simmonds' disease was established both clinically and pathologically.

3 In 158 cases the clinical picture seemed typical, but the patients were either still living or autopsy had not been obtained. We are inclined to believe that many of these were cases of anorexia nervosa.

4 The cardinal features of clinical Simmonds' disease are a), marked loss of weight, often progressing to cachectic emaciation, b), loss of sexual function—amenorrhea in the female, loss of libido and potency in the male, and usually sterility in both sexes, c), a low basal metabolic rate. Asthenia is also a common symptom but does not seem to have as much diagnostic significance.

5 It should be relatively simple to eliminate advanced tuberculosis, malignant disease, and thyrotoxicosis as causes of cachexia as none of these condi-

tions is associated with a low basal metabolic rate. Difficulty in differentiating Addison's disease from Simmonds' disease is rare.

6 The most difficult problem is the differentiation between true Simmonds' disease and anorexia nervosa. The occurrence of severe weight loss and a low basal metabolic rate in a young unmarried female who has never been pregnant favors the diagnosis of anorexia nervosa. Marked improvement or return to normal health as a result of psychotherapy or any other form of treatment available at present (endocrine therapy included), further suggests this diagnosis. A claim of cure in any case of true Simmonds' disease is open to doubt unless a pituitary tumor has been removed successfully.

The occurrence of severe weight loss, amenorrhea and a low basal metabolic rate in a woman over 30 years of age whose symptoms date from a postpartum hemorrhage and collapse, or whose sella turcica is deformed or contains calcification, and who in the course of the disease loses axillary and pubic hair, warrants a clinical diagnosis of Simmonds' disease.

Psychopathic disturbances favor the diagnosis of anorexia nervosa, but by no means exclude the possibility of the presence of true Simmonds' disease.

### CASE SUMMARIES

The following case reports on 9 patients who were seen by us appear in the literature for the first time.

Case 1 L.P. (group A) (University of California Clinic No. 48083), was a male, aged 19, whose chief complaint was inability to gain weight. Onset had been gradual at the age of 13 years when he had been 155 cm (5 ft 1 in) tall and had weighed 36.5 kg (80 lb). He had been somewhat weak since then, had noted occasional vertigo and headaches and his eyes had tired easily. He had had occasional erections but no libido. Two years before we saw him he had received 7 injections of anterior pituitary extract without definite effect. He had been drowsy frequently but had had no other psychic abnormalities.

On examination his height was 164 cm (5 ft 5 in) and his weight 30.5 kg (67 lb) [as compared to an ideal weight of 56.7 kg (125 lb)]. He was emaciated and had eunuchoid skeletal proportions. There was a downy growth of beard on his face and lanugo hair on his back. The extremities were tapering and cyanotic. The genitalia were small and no prostatic tissue could be felt by rectum. Blood pressure was 92/60 in the supine position and fell to 70/50 on standing. Temperature was 35.2°C (95.4°F). Laboratory tests were as follows: B.M.R., -34%, blood hemoglobin 74% (10.1 gm), Sahli, red blood cells, 4,500,000 per cu mm, white blood cells, 15,000 per cu mm with 2% eosinophiles, urine, normal, Blood Wassermann and Kahn reactions negative, glucose tolerance—fasting 80 mg %, ½ hr 167 mg %, 1 hr 187 mg %, 2 hr 100 mg %, 3 hr 86 mg %, 4 hr 63 mg %, 5 hr 75 mg %, plasma chlorides (as NaCl), 597 mg %, plasma cholesterol, 226

<sup>21</sup> Kylin (109-110) attempted to establish a separate syndrome for adolescent cases of Simmonds' disease which he termed late pubertal emaciation. We strongly suspect that many of these especially those in which the patients responded remarkably to treatment were actually instances of anorexia nervosa. Ryle (462) described a group of 33 cases of anorexia nervosa in young females from 15 to 29 years of age, the average age being 20 years.



mg. %; serum carotin, positive. Roentgenograms revealed that the bone age was 16 years and that the sella turcica was expanded and enlarged. The visual fields showed a temporal defect on the left.

The patient was operated upon by Dr. Howard Naffziger; an intrasellar Rathke's pouch cyst was drained and partially removed. Four months after operation no growth, appreciable weight-gain, or increase in sexual function had occurred and the B.M.R. had remained at  $-29\%$ . However, vision had improved and general strength had somewhat increased. At this time testosterone propionate therapy was instituted. The doses of 25 mg. were given hypodermically 3 times weekly and were increased to 50 mg. 3 times weekly after 3 months and continued at that level for another 3 months. As a result the patient grew 1 inch in height, gained 19 pounds in weight and noted considerable increase in general strength. Sexual function appeared with frequent erections and occasional emissions, and the external genitalia approximately doubled in size. His voice became deeper, he began to shave occasionally, and the hair growth on the body increased. Also the visual fields showed improvement. During the early part of the treatment, transient ankle edema and mild diabetes insipidus (intake to approximately 5 quarts daily) were noted but cleared up spontaneously. Testosterone therapy was selected because of disappointing results in other cases of Simmonds' disease from the administration of anterior pituitary extracts and because we were eager to ascertain whether the maturity-provoking effects of testosterone would indirectly stimulate the spurt of growth which normally occurs at puberty.

*Case 2. L.K., (group B) (Office No. 2588),* a 61-year-old housewife, had been seen first at the age of 53 years at which time her chief complaint had been insomnia. She stated at that time that she had never been well since the birth of her second child when she was 31 years old. Since then she had had headaches, backaches and slowing of her mental processes. She frequently had felt depressed and had always been cold. She had had a tendency to anemia for which she had received periodic treatment with various tonics and with thyroid substance. Her skin and hair had become dry. Catamenia had ceased suddenly without menopausal symptoms when she was 34 years old. She had lost 18 pounds of weight in the preceding 3 years. Upon examination her height had been  $59\frac{1}{2}$  inches and her weight 118 lb. (ideal weight, 128 lb.). Her face had been slightly puffy and the eyebrows had been thin. The hair had been dry and scant in the axillary and pubic regions. Her tongue had been smooth and the nails brittle. Heart rate had been 66 per minute; blood pressure, 142/64. Laboratory tests had shown: hemoglobin,  $73\%$ ; red blood cells, 3,820,000 per cu. mm. B.M.R.  $-27.7\%$ . Fluoroscopy of the chest had revealed no abnormalities. On an increased dose of thyroid and occasional iron and liver extracts, she had improved somewhat.

After 8 years she returned to us complaining of exhaustion and loss of weight. At this time she weighed 95 lb., her skin was pale, dry and wrinkled and her hair was dry and thin; her pulse rate was 50 per minute and her blood pressure 150/30. Glucose tolerance test results were as follows: fasting, 97 mg. %;  $\frac{1}{2}$  hr., 142 mg. %; 1 hr. 162

mg. %; 2 hr. 97 mg. %; 3 hr., 109 mg. %; 4 hr., 123 mg. %; 5 hr., 63 mg. %. The dose of thyroid was increased to 4 grains daily, but the patient's weight dropped to 94 lb. so that she was 42 lb. underweight. She was then hospitalized and insulin was administered, 5 u three times daily and then 10 u three times daily. As the latter dose caused reactions, it was reduced to 5 u twice daily. Anterior pituitary growth extract in 2 cc. doses 3 times weekly and later thyroid, 2 grains daily, were added. On this regime she improved somewhat and her weight gradually increased to 100 lb. She died 2 years later of sudden heart failure. No autopsy was performed.

*Case 3. M.C., (group B) (Office No. 6248),* a 31-year-old housewife, was first seen with complaints of loss of weight and asthenia. The onset had occurred 6 years before, 3 years after the birth of her only child, and had been accompanied by amenorrhea and loss of libido. Asthenia and some diminution of appetite had followed and within 5 years she had lost 62 lb. Two years before we saw her she had received thyroid substance and, for a short period, anterior pituitary extract injections and anterior pituitary substance orally, but no definite improvement had taken place. Other symptoms were: occasional frontal headaches, softening of the teeth, sensitivity to cold and some dryness of the skin and hair. She had become slow and negativistic.

The patient was  $64\frac{1}{4}$  in. tall. She was extremely emaciated, weighing 64 lb. (70 lb. under ideal weight). The body temperature was  $97^{\circ}$  F. The heart rate varied between 44 and 53 beats per minute; blood pressure was 80-86/60. The breasts were small and the internal and external genitalia were atrophic. Some hypertrichosis was observed on the thighs and lower back. Laboratory investigation gave the following results: blood hemoglobin,  $69\%$  (Sahli); red blood cells, 3,310,000 per cu. mm.; white blood cells, 4,900 per cu. mm. with  $1\%$  eosinophiles; blood Kahn reaction, negative; B.M.R.,  $-45\%$ .

The patient did not cooperate in continuing either investigation or treatment.

*Case 4. R.M., (group C) (Office No. 5340),* a male newspaper worker aged 20, was first seen on Feb. 7, 1936, at which time his chief complaint was loss of hair. Onset had been 10 months before when he had sustained a fractured skull in an automobile accident. He had been unconscious for 5 weeks and now had a residual paralysis of the right side of the face, and an aneurism of the right internal carotid artery which caused a bulging of the right eye. He also had diabetes insipidus with an intake of 11 quarts of fluid daily. Other symptoms were daytime drowsiness, moderate anorexia, diminution of libido, moderate asthenia and loss of 33 pounds. He displayed no psychic changes other than those which would be expected as a result of a disfiguring accident. In the preceding 2 months he had lost considerable hair from legs and face.

The patient weighed 141 lb. (7 lb. underweight) and was 69 in. tall. In addition to the right facial paralysis he had exophthalmos on the right with diminished vision and pallor of the optic disc on that side. His skin was dry and somewhat pale. Hair was absent from the face, the extremities and axillary regions. The pubic hair was scant

and of feminine distribution. Heart sounds were regular, the rate being 72 per minute, blood pressure was 84/50. The genitalia were small. Laboratory tests showed blood hemoglobin, 72%, red blood cells, 4,430,000 per cu mm, white blood cells 7,100 per cu mm with 3% eosinophiles, B M R -17 mg %,  $\frac{1}{2}$  hr, 135 mg  $\frac{1}{2}$ , 3 hr, 78 mg %, 4 hr, 53 mg %, 5 hr, 58 mg %.

Treatment with anterior pituitary growth extract was instituted and later pituitary gonadotropin was tried. On this regime the patient gained a little weight and had a slight increase in growth of hair. He was then given thyrotropic hormone without definite effect. On Nov 16, 1936, Dr Howard Fleming ligated the right common carotid artery. As a result moderate improvement of local symptoms in the head occurred, and after a period of 4 months the patient's weight and strength had increased slightly.

Case 5 V D, (group C) (Office No 5672), an 18 year-old girl, a student, was first seen on Nov 24, 1936, complaining of asthenia, nervousness, palpitation, and inability to gain weight. Two years before she had noted that she tired easily and in the past year had lost 13 lb. Her menstrual periods had been regular until the last one which had been delayed 2 weeks. In the last year her teeth had become soft and she had had occasional frontal headaches. No psychic disturbances except the nervousness had occurred. On examination the patient appeared short and thin. Her height was 61 in and her weight 89 lb (26 lb underweight). She looked rather young for her age. Moderate hypertrichosis was observed. The heart rate was regular at 90, blood pressure, 90/50. Laboratory tests showed blood hemoglobin, 94%, red blood cells, 4,580,000 per cu mm, white blood cells, 5,600 per cu mm with 1% eosinophiles, B M R, -23.4%, uric acid and stool examinations, normal, glucose tolerance test, fasting, 85 mg %,  $\frac{1}{2}$  hr, 115 mg %, 1 hour, 102 mg %, 2 hr, 83 mg %, 3 hr 80 mg %, 4 hr, 89 mg %, 5 hr, 57 mg %. Treatment was instituted with adrenal cortical extract in doses of 1 cc and later 2 cc daily. After 1 month of this therapy her weight had dropped to 87 $\frac{1}{2}$  lb, whereupon she received anterior pituitary extract in doses of 1 cc daily. As this treatment produced no definite effect, insulin therapy was instituted in gradually increasing doses. In 5 months she had gained to 97 $\frac{1}{2}$  lb and her general strength had improved, but her teeth were still poor and her menses irregular. She then received calcium and cod liver oil, and later insulin and estrogen therapy was resumed. Nevertheless, her condition remained practically unchanged.

Case 6 J L, (group C) (Office No 5860), was a 50-year-old unmarried male accountant who was first seen on May 13, 1937 complaining of blurring of vision and impotence. He had had mumps without complications at the age of 16. His last successful intercourse had occurred 2 years before and he had had occasional emissions since then. However, he had gradually lost libido and an attempted intercourse 2 weeks before had been unsuccessful. He had lost 27 lb in the past 2 years, had developed some asthenia and had become moderately depressed. Vision in

the left eye had gradually diminished for the past year. Examination showed him to be thin and pale with a cadaverous appearance. His height was 69 in, his weight, 115 $\frac{3}{4}$  lb (51 lb underweight). His skin was dry with some increase of pigmentation in the folds. His hair was dry but of normal thickness. He had bilateral cataracts. His heart beat was regular with a rate of 76, blood pressure was 90/68. The right testicle was considerably smaller than the left. Laboratory tests showed blood hemoglobin, 68%, red blood cells, 3,640,000 per cu mm, white blood cells, 6,500 per cu mm with 2% eosinophiles, blood Kahn reaction, negative, B M R, +6.5%. A previous examination had revealed achlorhydria. Treatment with testosterone propionate injections 3 times weekly and dilute hydrochloric acid was begun. As no definite effects were noted, therapy with gonadotropic hormone 3 times weekly was instituted. After 4 weeks of this treatment his weight had dropped to 113 $\frac{1}{2}$  lb and he felt no better. Adrenal cortex extract injections 3 times weekly were then added to his regime, but he did not improve. His course was complicated by recurrent diarrhea.

Case 7 S H, (group F) (Laguna Honda Home, University of California Service of Dr LeRoy Briggs, case No 21567), was a Nicaraguan house maid aged approximately 43 years. Nine months before we first saw her she had had tuberculous pleurisy with effusion and minimal tuberculosis of both lung apices. She had responded well to treatment at the San Francisco Hospital but as she had continued to be markedly asthenic and underweight, she had been referred to the Laguna Honda Home. She had had amenorrhea for 6 months.

The patient was emaciated. She weighed only 73 $\frac{1}{2}$  lb (59 lb underweight) while her previous weight had been 127 lb. Her height was 60 $\frac{1}{4}$  in. She was apathetic. The hair growth over her chin was increased. The skin, in addition to the racial pigmentation, showed a few spots of increased pigment over the face. Blood pressure was 100/60 and ranged as low as 86/54. Tenderness and spasm were elicited over the left lower quadrant of the abdomen. Laboratory tests showed the following B M R, -29% (recheck, -31%), plasma chlorides, 510 mg % (recheck, 573 mg %), glucose tolerance test, fasting 77 mg %,  $\frac{1}{2}$  hr, 143 mg %, 1 hr, 189 mg %, 2 hr, 139 mg %, 3 hr, 83 mg %, 4 hr, 44 mg %, 5 hr, 52 mg %, 6 hr, 93 mg %. Roentgenograms of the chest showed old healed tuberculosis of the left apex and thickening of the pleura on the right, abdominal films showed no calcifications, the sella turcica was normal, gastrointestinal series showed an atonic stomach but no other abnormalities.

On a salt free diet no Addisonian crisis occurred. As treatment with adrenal cortex extract and thyroid was ineffective, anterior pituitary extract was administered in doses of 1 cc daily. After 4 months the patient's weight had gradually increased to 96 lb. At this time insulin was added to the regime and after another 4 months the patient's weight had increased to 107 lb (a total gain of 33 $\frac{1}{2}$  lb), nevertheless she remained apathetic. Her menses had returned some time during the preceding 3 or 4 months. Her condition otherwise remained stationary under intermittent treatment with anterior pituitary extract, but the psychic symptoms became more marked and she

had occasional spells of disorientation at one time suggesting a catatonic schizophrenia. It became difficult to make her take food and her course started gradually downward in spite of treatment with benzedrine and later with a different preparation of anterior pituitary extract. She had occasional attacks of abdominal pain and nausea which could not be controlled by increased salt intake. About a year later her weight dropped to 85 lb. and she spent most of the time in bed. Cough and fever developed and tubercle bacilli were found in the sputum. After a short febrile course she died in coma.

Autopsy revealed extensive caseous tuberculosis of both lungs and tuberculosis of the ileum. The pituitary was normal in gross and microscopic appearance. The thyroid weighed 8.5 gm. and showed adenomata. The two adrenals weighed 9.5 gm. and showed moderate cortical hyperplasia and one small adenoma. The ovaries were fibrotic and the uterus was small.

Case 8. M.S., (group H) (Office No. 6357), was a girl, a student, aged 19 years and 4 months, who was first seen on Nov. 1, 1938, with a chief complaint of weakness. She had been overweight, reaching 160 lb. at the age of 12, and had been sensitive to taunts about being fat. She had dieted and lost weight to 130 lb. at the age of 14. She remained at this level until she was 16 years of age (3 years before we saw her) at which time she had a mild febrile illness following which she became asthenic and depressed. Her appetite diminished, she began to vomit after meals and had epigastric distress. Amenorrhea had developed suddenly with the onset of the illness. At that time her B.M.R. was recorded as  $-31\%$  and her blood sugar as low.

Two years before we saw her, a diagnosis of Simmonds' disease had been made by a well-known internist in the Middle West and she had been treated for a time with anterior pituitary preparations. Only slight improvement had resulted. However, a series of chiropractic manipulations had been of considerable benefit and she had gained in weight from 89 to 115 lb. She had gradually lost some of this weight and her weakness had increase to the point at which she had to stop school. She had a compulsion to vomit after every meal and at times requested her mother to help her prevent this. At that time she was travelling about in search of a 'cure.' When we examined her she was thin and somewhat pale. Her height was  $65\frac{3}{8}$  in. and her weight 104 lb. (25 lb. underweight). Her skin was dry, her hair was coarse and rather scant in the axillary and pubic regions. Her breasts were small and the internal genitalia somewhat atrophic. Her pulse rate was 48 beats per minute and her blood pressure 78/40. Laboratory examinations revealed: hemoglobin, 68%; red blood cells, 3,190,000 per cu. mm.; white blood cells, 3,050 per cu. mm. with 2% eosinophiles; B.M.R.,  $-19\%$ . On a regime of forcing food, the patient gained 6 lb. in a week.

Case 9. M.A., (group H) (Office No. 5905), a school girl aged 16 years and 9 months, was first seen on June 18, 1935. Her chief complaints were irregular menses and inability to gain weight. She had had pleurisy with effusion at the age of 7. Menses had always been irregular

since the menarche at 14 and she had had complete amenorrhea for 2 years. Her weight had been 127 lb. 1 year before we saw her and had dropped to 97 lb. 8 months before because she would not eat. On examination the patient was thin and had disproportionately long extremities. Her height was 64 in. and her weight 109  $\frac{1}{4}$  lb. (22 lb. underweight). She had a small adolescent goiter, and the pubic hair was scant. Blood pressure was 72/50. Laboratory tests showed: hemoglobin, 93% red blood cells, 5,190,000 per cu. mm.; eosinophiles, 1%; B.M.R.,  $-5\%$  and  $-14\%$ . Roentgenograms of the gastrointestinal tract showed evidences of aerophagia. Further investigation revealed that she was deeply emotional and had been subjected to considerable 'nagging' at home; also, that she was feeling neglected socially. Home treatment was tried without any benefit and a year later we learned that the patient was in a mental hospital in a hypomanic state.

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# The Quantitative Variations of the Pancreatic Islet Tissue in a Mixed Series of Cases

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A HISTOLOGICAL SURVEY of the pancreas in a large series of unselected cases quickly discloses the fact that the amount of islet tissue varies a great deal from case to case. Heilberg (1), and later, Ogilvie (2), devised methods for estimating the weight of an average islet and also the number of islets in a given pancreas. From these data it was possible, too, to calculate by weight, the proportion of islet tissue in the pancreas. These figures were arrived at through area readings.

Ogilvie's work has been confined to the creation of normal standards, and to the age variations. In the present series, however, the chief consideration is the possible effects of disease on the amount of islet tissue present.

## METHODS

The amount of islet tissue in each section was estimated by area readings made with a planimeter. In a number of cases readings were made on sections from several parts of the same pancreas, these readings corresponded so closely as to confirm the view that islet tissue is distributed fairly uniformly, and that readings from any one section were representative.

All of the islets in 10 standard fields of each section, chosen at random, were drawn under the low power ( $\frac{2}{3}$ ) by the camera lucida. The islet areas in each field were then calculated with a planimeter. The whole field including both islet and acinar tissue measured 110 planimeter units. One planimeter unit was equivalent to 118 square centimeters of the camera lucida drawings, and these drawings had been magnified to 77.8 times the original size in the sections. At first the results were classified on the basis of planimeter units but this was altered eventually to the percentage of islet tissue to pancreatic tissue as a whole, for this reason the percentage unit for the various groups may appear unusual. The follow-

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ing table gives the corresponding planimeter unit (P.U.) and percentage values

1 P.U. = 0.9 per cent, 2 P.U. = 1.8 per cent, 3 P.U. = 2.7 per cent, 4 P.U. = 3.6 per cent, 5 P.U. = 4.6 per cent and 6 P.U. = 5.5 per cent

## MATERIAL

The present series consists of 202 unselected cases in which sections of the pancreas were available. Of these 202 cases, 5 were without complete details,

TABLE 1 AGE AND SEX DISTRIBUTION OF DIABETICS AND THE WHOLE SERIES

| Age Group, years | Male           |              | Female         |              | Totals         |              |
|------------------|----------------|--------------|----------------|--------------|----------------|--------------|
|                  | Diabetic group | Whole series | Diabetic group | Whole series | Diabetic group | Whole series |
| 0-9              | 1              | 23           | 0              | 8            | 1              | 31           |
| 10-19            | 0              | 5            | 0              | 5            | 0              | 10           |
| 20-29            | 3              | 7            | 9              | 20           | 12             | 27           |
| 30-39            | 0              | 3            | 7              | 15           | 7              | 18           |
| 40-49            | 3              | 19           | 3              | 16           | 6              | 35           |
| 50-59            | 4              | 25           | 4              | 14           | 8              | 39           |
| 60-69            | 6              | 18           | 4              | 13           | 10             | 31           |
| 70+              | 1              | 4            | 2              | 3            | 3              | 6            |
| No details       |                |              |                | 1            | 4              | 5            |
| Totals           | 18             | 103          | 29             | 94           | 51             | 202          |

leaving 197 cases with all the necessary data. The full series contained 51 diabetics but 4 had incomplete information available leaving 47 cases in all, for parts of this investigation. Nondiabetics with full data numbered 150. The sections had been prepared by the paraffin method and stained by haemalum and eosin. The age and sex distribution is shown in table 1.

## RESULTS

After inspecting the results it became obvious that there was a number of cases with very low readings, and it seemed that these might constitute a definite group, possibly associated with diabetes mellitus.

### Cases with Low Islet Tissue Content

**Diabetic group.** Although the normal range of islet area readings is discussed later in detail, a summary of those findings is essential at this stage in order to provide a normal standard. In adults the majority of the islet readings were between 0.9 and 2.7 per cent, while in infants the range was between 0.9 and 3.6 per cent of islet tissue per field of pancreas. For the purposes of this investigation it is assumed that

TABLE 2. AGE AND SEX ANALYSIS OF DIABETIC CASES WITH READINGS UNDER 1.36 PER CENT

| Age Group, years | Male   |           | Female |           | Totals |           |       |
|------------------|--------|-----------|--------|-----------|--------|-----------|-------|
|                  | 0-0.9% | 0.9-1.27% | 0-0.9% | 0.9-1.27% | 0-0.9% | 0.9-1.27% | Total |
| 0-9              | 1      | 0         | 0      | 0         | 1      | 0         | 1     |
| 10-19            | 0      | 0         | 0      | 0         | 0      | 0         | 0     |
| 20-29            | 1      | 1         | 7      | 2         | 8      | 3         | 11    |
| 30-39            | 0      | 0         | 5      | 1         | 5      | 1         | 6     |
| 40-49            | 1      | 2         | 1      | 1         | 2      | 3         | 5     |
| 50-59            | 1      | 2         | 2      | 1         | 3      | 3         | 6     |
| 60-69            | 3      | 1         | 2      | 1         | 5      | 2         | 7     |
| 70+              | 1      | 0         | 2      | 0         | 3      | 0         | 3     |
| No details       |        |           |        |           | 2      | 2         | 4     |
| Totals           | 8      | 6         | 19     | 6         | 29     | 14        | 43    |

these constitute the normal limits in adults and in infants respectively. With these basic standards available it is possible to appreciate the findings in the diabetic group.

There were 51 cases of diabetes mellitus in this series, of which the age and sex distribution is shown in table 1.

Of the 51 cases in the diabetic group

29 had islet area readings under 0.9 per cent; 14, with readings between 0.9 and 1.3 per cent; 2, with readings between 1.4 and 1.7 per cent; 4, with readings between 1.8 and 2.6 per cent; 1, with readings between 2.7 and 3.6 per cent and 1, with readings over 4.6 per cent.

Over one-half of the diabetic cases, 29 in all, have islet area readings under 0.9 per cent, while 43 of the total of 51 cases are under 1.3 per cent. The arithmetic average of the area readings in the 51 diabetic cases is 0.99 per cent with the readings ranging from 0.17 to 4.6 per cent; 22 cases had values over 0.9 per cent including 16 with readings between 0.9 and 1.8 per cent. As these 16 cases constitute the bulk of diabetics with higher readings, they can be considered separately. Six showed hyalin degeneration varying from scattered patches to extensive involvement of many islets; others had congestion, hemorrhage, atheroma, or partial fibrosis of the islets. Thus, these high readings are not necessarily due to healthy or functioning islet tissue. If allowance is made for this fact it becomes evident that the typical case of dia-

betes mellitus had an average islet tissue value of under 0.9 per cent.

Diabetic cases with readings over 1.8 per cent numbered 6 in all. Of these, 2 showed extensive islet degeneration, and 1 extensive islet hemorrhage. In the remaining 3 cases there was nothing extraneous to account for the high readings. One was a case that had not been active for 5 years (reading 2.1%); the possibility exists that here islet tissue repair had taken place in the form of hyperplasia. A similar explanation might account for the high readings in the remaining 2 cases.

**Nondiabetic cases with readings under 0.9 per cent.** The whole series included 4 nondiabetics with readings under 0.9 per cent. Details concerning these cases are available in table 3.

Thus, readings under 0.9 per cent are highly suggestive of diabetes mellitus. The whole series contained only 4 nondiabetics (2%) with these low readings, while Ogilvie's series had 4 per cent of cases of this type. In view of the absolute predominance of diabetics among these cases, the 'under 0.9 per cent' group can be considered with justification to constitute a section showing islet tissue deficiency.

### Cases with a Normal Range of Islet Tissue Content

In order to establish what constitutes the normal islet tissue content, two methods are available; a) the readings in cases in which the disease of the patient had not had sufficient time to cause any appreciable islet changes could be considered to be within normal limits; b) it could be assumed that as the greater proportion of cases in an unselected series

TABLE 3. NONDIABETIC CASES WITH READINGS UNDER 0.9 PER CENT

| Case | Sex, Age | Disease                             | Islet Area Values, % |
|------|----------|-------------------------------------|----------------------|
| 48   | F 23     | Diabetes insipidus                  | 0.86                 |
| 172  | M 53     | Lobar pneumonia                     | 0.77                 |
| 217  | M 51     | Myocardial failure                  | 0.68                 |
| 386  | M 58     | Acute pericarditis, adrenal atrophy | 0.72                 |

will have normal readings, an examination of the frequencies of the readings in the whole series might be of value. Adults and infants are studied separately.

**Adults.** An appreciable increase in the amount of islet tissue could occur only through hypertrophy or hyperplasia or both, and some time would necessarily elapse before these processes could be established. Hence an increased islet tissue content could be expected only in association with chronic diseases, while in cases of acute diseases the amount of islet tissue present is more likely to be within normal limits. There is the possibility, however, that some long-

standing process, not of a disabling character and of the type that might have been overlooked at a post-mortem examination, could have altered the islet tissue content in what appeared to be an acute case. This possibility must be kept in mind.

In the present series there were 23 cases of acute disease with no obvious chronic complications. Of these, 10 were males and 13 females. The readings obtained in this group were as follows.

1 with average reading under 0.9 per cent, 18 with average reading between 0.9 and 1.8 per cent, 3 with average reading between 1.8 and 2.7 per cent, and 1 with average reading between 2.7 and 3.6 per cent.

Accordingly, readings between 0.9 and 1.8 per cent probably represent the normal range in islet tissue content. This is further implied by the arithmetic average of 1.6 per cent for the 23 cases.

The problem can be approached from another direction. It is reasonable to suppose that in most of the nondiabetic cases in the whole series the amount of the islet tissue will not be seriously disturbed. If this be so, then an examination of the incidence of the islet tissue values might give some indication as to what constitutes the normal range.

Among the nondiabetic cases excluding infants there were

4 with readings under 0.9 per cent, 64 with readings between 0.9 and 1.8 per cent, 46 with readings between 1.8 and 2.7 per cent, 22 with readings between 2.7 and 3.6 per cent, 6 with readings between 3.6 and 4.6 per cent, 5 with readings between 4.6 and 5.5 per cent, and 5 with readings over 5.5 per cent.

The 0.9 to 1.8 per cent group shows the highest frequency (35%) while the 1.8 to 2.7 per cent group claims 25 per cent. Both groups combined account for 60 per cent of all of the adult cases. Hence, it can be assumed with safety that the normal range lies between 0.9 and 2.7 per cent while over 3.6 per cent might be considered high.

*Infants.* In all, there were 25 cases under 3 years of age; 21 were under one year and 4 were between 1 and 2 years. As all but 4 of the cases were under one year of age, observations on the infant group were limited to this section. Of the cases under one year of age there were

7 with readings between 0.9 and 1.8 per cent, 7 with readings between 1.8 and 2.7 per cent, 3 with readings between 2.7 and 3.6 per cent, 1 with readings between 3.6 and 4.6 per cent, 1 with readings between 4.6 and 5.5 per cent, and 2 with readings between 5.5 and 6.4 per cent.

Fourteen or two-thirds of these cases had readings up to 2.7 per cent, and 17 up to 3.6 per cent. The arithmetic mean for the values in these 21 cases was 2.5 per cent with readings from 1.1 to 5.6 per cent. Thus the indications are that the normal range in the infant group is between 0.9 and 2.7 per cent, and this probably should be extended to cover the 2.7 per cent group as well (up to 3.6%). Therefore, one may

conclude that there appears to be a tendency for the higher readings to be more frequent among infants. That the normal for infants is higher than that for adults is indicated by the results obtained by Ogilvie. This is further supported by the clinical evidence of various workers that the blood sugar in infants is lower than in adults.

TABLE 4. DETAILS OF CASES WITH ISLET AREA READINGS OVER 3.6 PER CENT

| No. of Cases | Islet Group   | Case | Sex, Age | Disease                                      | Islet Reading <sup>1</sup> |
|--------------|---------------|------|----------|--|----------------------------|
| 7            | 3.6 to 4.6%   | 28   | M, 66    | Pulm. tuberc.                                | 4.4                        |
|              |               | 115  | M, 3 mo. | Acute broncholitis                           | 3.7                        |
|              |               | 173  | M, 55    | Pericarditis                                 | 3.8                        |
|              |               | 193  | M, 45    | Syphilitic aortitis                          | 4.2                        |
|              |               | 205  | F, 7     | Chloroma                                     | 3.7                        |
|              |               | 332  | F, 54    | C.M.F., atrophy of thyroid                   | 4.0                        |
|              |               | 351  | M, 18    | Addison's disease, ulc. enteritis            | 4.0                        |
| 6            | 4.6 to 5.4%   | 31   | M, 12    | Tuberc. of spine, bronchopneumonia           | 5.2                        |
|              |               | 188  | M, 6 mo. | Lymphosarcoma, cap bronchitis                | 4.8                        |
|              |               | 211  | F, 43    | Otitis media, cerebral abscess, pyemia       | 4.9                        |
|              |               | 215  | F, 58    | Carc. esophagus                              | 5.1                        |
|              |               | 270  | M, 48    | Cerebral hemorrhage, acute encephalitis      | 5.2                        |
|              |               | 376  | M, 62    | Diabetes mellitus, chronic Pb poison, pyemia | 4.6                        |
| 7            | 5.5% and over | 51   | M, 61    | Chr. pulm. tuberc.                           | 11.6                       |
|              |               | 91   | M, 56    | Pellagra, carc. of tongue                    | 7.8                        |
|              |               | 329  | M, 3 mo. | Cerebrospinal meningitis                     | 5.5                        |
|              |               | 337  | M, 41    | Ulc. colitis                                 | 6.2                        |
|              |               | 342  | F, 5 mo. | Bronchopneumonia                             | 5.6                        |
|              |               | 349  | M, 1     | Bronchopneumonia                             | 7.6                        |
|              |               | 359  | M, 40    | Chr. myeloid leuk.                           | 6.2                        |

<sup>1</sup> Percentage ratio of islet tissue to pancreas.

### Cases with High Islet Tissue Content

After excluding all the cases with readings up to 3.6 per cent, those that remain can be considered definitely as of the high islet tissue content group. In all there were 20 such cases and their details are presented in tables 4 and 5.

Table 5 shows that there were no cases of this type between 20 and 40 years of age which suggests the existence of two distinct groups, one under 20 years and another over 40 years of age.

There were 8 cases under 20 years of age. Of these 5 were one year of age or under, and all were cases showing acute diseases unlikely to affect the islet tissue quantitatively, hence it can be assumed that the high readings were of congenital origin.

A disease analysis of the group of 20 cases showed that tuberculosis had claimed 3, pernicious anemia and other blood diseases 3, and malignant disease 3 cases each. These, together with the 5 cases of one

TABLE 5. AGE AND SEX INCIDENCE OF CASES WITH AVERAGE ISLET AREA PER FIELD VALUE OVER 3.6 PER CENT

| Age Group, years | Male | Female | Total |
|------------------|------|--------|-------|
| 0-1              | 3    | 1      | 4     |
| 1-9              | 1    | 1      | 2     |
| 10-19            | 2    | 0      | 2     |
| 20-29            | 0    | 0      | 0     |
| 30-39            | 0    | 0      | 0     |
| 40-49            | 4    | 1      | 5     |
| 50-59            | 2    | 2      | 4     |
| 60-69            | 3    | 0      | 3     |
| 70+              | 0    | 0      | 0     |
| Totals           | 15   | 5      | 20    |

year of age and under, account for 13 of the 20 cases (one case was included in two groups).

If the arithmetic means for the group of cases with acute diseases can be taken as the normal reading, then it becomes evident (table 6) that in blood diseases, malignant diseases, tuberculosis, syphilis, and even in chronic diseases as a whole, the average is about twice that for the normal. The disease conditions in these groups are for the most part diseases of the chronic and proliferative types. In the process of cell proliferation an increased demand for carbohydrate has been observed, and it may be that the apparent association of chronic diseases with an increased islet tissue content is brought about by an increased carbohydrate metabolism.

Islet Tissue Content in Relation to Size and Number of Islets

Variation in islet tissue content can only occur through alterations in the size or in the number of

islets, or both. Accordingly, it was found necessary to make analyses based on these features. The following tables give the available data furnished by this series of cases in respect to both the size and the number of pancreatic islets in a standard area (tables 7-12). Although the complete series is made up of 202 cases, all necessary details are available in 197, of which 47 are diabetics. The following tables are based, therefore, on the findings in 150 nondiabetics and 47 diabetics. The size of the average islet is measured in planimeter units (p.u.).

*Nondiabetics.* The group of nondiabetics is sufficiently large to give some idea as to the size and the number of islets in a normal pancreas.

TABLE 6. COMPARISON OF ARITHMETIC AVERAGE OF ISLET AREA READINGS PER FIELD IN VARIOUS DISEASE GROUPS

| Disease Groups       | Islet Area Reading Over % | No. of Cases |
|----------------------|---------------------------|--------------|
| Acute disease        | 1.6                       | 23           |
| Infants under 1 year | 2.5                       | 21           |
| Aplastic anemia      | 1.9                       | 4            |
| Blood diseases       | 2.8                       | 13           |
| Malignant disease    | 3.1                       | 14           |
| Tuberculosis         | 3.2                       | 14           |
| Syphilis             | 3.3                       | 3            |
| Chronic diseases     | 3.1                       | 42           |

A. Under 10 years of age (10% of nondiabetics). All except 2 of the 30 cases under 10 years of age had 50 or more islets in 10 fields; 20 of the 21 cases under one year belonged to this group (table 7). The average size of islets was between 0.2 and 0.4 p.u. except in 4 cases. There was none over 0.6 p.u., that is, of the enlarged type (table 10).

B. Over 10 years of age (80% of nondiabetics). In direct contrast with the foregoing are those groups of cases over 10 years of age. Fifty-one per cent had between 20 and 50 islets in 10 microscopic fields, while

TABLE 7. ANALYSIS OF 150 NONDIABETICS ACCORDING TO AGE GROUPS AND THE NUMBER OF ISLETS IN 10 MICROSCOPIC FIELDS

| No. of Islets in 10 Fields | Age Groups in Years |     |     |       |       |       |       |       |       |     | Total | %   |
|----------------------------|---------------------|-----|-----|-------|-------|-------|-------|-------|-------|-----|-------|-----|
|                            | 0-1                 | 1-3 | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70+ |       |     |
| 10-19                      |                     |     |     |       |       |       |       | 1     |       |     | 1     | 1   |
| 20-29                      |                     |     |     | 1     | 1     | 4     | 3     | 6     | 0     | 1   | 16    | 11  |
| 30-39                      |                     |     |     | 4     | 7     | 2     | 4     | 7     | 6     | 0   | 30    | 20  |
| 40-49                      | 1                   | 0   | 2   | 2     | 4     | 2     | 8     | 5     | 6     | 1   | 30    | 20  |
| 50-59                      | 4                   | 0   | 5   | 1     | 2     | 0     | 2     | 4     | 4     | 0   | 18    | 12  |
| 60-69                      | 5                   | 2   | 7   | 0     | 0     | 2     | 6     | 4     | 1     | 1   | 21    | 14  |
| 70-79                      | 4                   | 0   | 4   | 0     | 1     | 0     | 1     | 2     | 3     | 0   | 11    | 7   |
| 80-89                      | 1                   | 1   | 2   | 0     | 0     | 0     | 2     | 0     | 0     | 0   | 4     | 3   |
| 90-99                      | 1                   | 0   | 2   | 0     | 0     | 1     | 0     | 0     | 0     | 0   | 3     | 2   |
| 100-199                    | 4                   | 0   | 6   | 2     | 0     | 0     | 3     | 2     | 0     | 0   | 13    | 9   |
| 200-299                    | 1                   | 1   | 2   | 0     | 0     | 0     | 0     | 0     | 0     | 0   | 2     | 1   |
| 300-399                    | 0                   | 0   | 0   | 0     | 0     | 0     | 0     | 0     | 1     | 0   | 1     | 1   |
| Totals                     | 21                  | 4   | 30  | 10    | 15    | 11    | 29    | 31    | 21    | 3   | 150   | 100 |

a further 37 per cent were dispersed among the higher groups (table 7). The size of the average islets in over 40 per cent of the cases was between 0.4 and 0.6 P.U. while a further 26 per cent was in the 0.3 P.U. section (table 10).

It seems, therefore, that among the nondiabetics as a whole there are two distinct standards, the one for children under 10, and the other for the higher age groups.

The above data disclose these further points. In 11 per cent of the cases in the nondiabetic group the average size of islets was definitely above the normal range (over 0.7 P.U., table 10), and with the exception of one case these were all over 20 years of age. Furthermore, enlarged islets were present in all adult age groups, in contrast with the diabetics in whom essentially enlarged islets are found in cases over 40 years of age (table 11).

### Disease Groups

*Diabetes mellitus (47 cases)* Seventy-six per cent of the 47 cases of diabetes mellitus had from 10 to 30

TABLE 8 ANALYSIS OF 47 DIABETICS ACCORDING TO AGE GROUPS AND THE NUMBER OF ISLETS IN 10 MICROSCOPIC FIELDS

| No of Islets in 10 Fields | Age Groups in Years |       |       |       |       |       |       |     | Total | %   |
|---------------------------|---------------------|-------|-------|-------|-------|-------|-------|-----|-------|-----|
|                           | 0-9                 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70+ |       |     |
| 10-19                     | 0                   | 0     | 5     | 3     | 2     | 3     | 3     | 2   | 18    | 38  |
| 20-29                     | 1                   | 0     | 5     | 4     | 2     | 2     | 3     | 1   | 18    | 38  |
| 30-39                     | 0                   | 0     | 1     | 0     | 2     | 1     | 2     | 0   | 6     | 13  |
| 40-49                     | 0                   | 0     | 1     | 0     | 0     | 1     | 0     | 0   | 2     | 4   |
| 50-59                     | 0                   | 0     | 0     | 0     | 0     | 1     | 2     |     | 3     | 7   |
| Totals                    | 1                   | 0     | 12    | 7     | 6     | 8     | 10    | 3   | 47    | 100 |

islets in 10 fields (table 8) while in 81 per cent the average islets measured from 0.1 to 0.6 P.U. (table 11). Six per cent had average islets between 0.1 and 0.19 P.U., a range exclusively limited to diabetic cases. In 19 per cent the average islets were from 0.6 to 1.0 P.U. and these were chiefly cases over 50 years of age.

Thus, in diabetics, normal sized and small islets are common. The incidence of enlarged islets is no greater than among nondiabetics although in diabetics

TABLE 9 ANALYSIS OF A NUMBER OF DISEASE GROUPS AND ISLET AREA GROUPS ACCORDING TO THE NUMBER OF ISLETS IN 10 MICROSCOPIC FIELDS

| No of Islets in 10 Fields | Acute Diseases | Aplastic anemia | Malignant Disease | Tuberculosis | Blood Disease | Syphilis | Non-diabetics under 0.9% | Cases 3.6-4.6% | Cases 4.6-5.5% | Cases over 5.5% |
|---------------------------|----------------|-----------------|-------------------|--------------|---------------|----------|--------------------------|----------------|----------------|-----------------|
| 20-29                     | 7              | 1               | 1                 | 1            | 0             | 0        | 3                        | 0              | 0              | 0               |
| 30-39                     | 6              | 1               | 3                 | 3            | 3             | 0        | 1                        | 0              | 1              | 0               |
| 40-49                     | 7*             | 2               | 0                 | 3            | 4             | 0        | 0                        | 0              | 0              | 0               |
| 50-59                     | 2              | 0               | 4                 | 2            | 1             | 0        | 0                        | 0              | 1              | 0               |
| 60-69                     | 1*             | 0               | 3                 | 0            | 2             | 0        | 0                        | 1              | 2              | 0               |
| 70-79                     |                | 0               | 1                 | 1            | 1             | 2        | 0                        | 3              | 0              | 0               |
| 80-89                     |                | 0               | 0                 | 1*           | 1             | 0        | 0                        | 0              | 0              | 1               |
| 90-99                     |                | 0               | 0                 | 0            | 0             | 0        | 0                        | 0              | 0              | 0               |
| 100-199                   |                | 0               | 2*                | 2*           | 1*            | 1        | 0                        | 3**            | 2*             | 3*              |
| 200-299                   |                | 0               | 0                 | 0            | 0             | 0        | 0                        | 0              | 0              | 2**             |
| 300-399                   |                | 0               | 0                 | 1            | 0             | 0        | 0                        | 0              | 0              | 1               |
| Totals                    | 23             | 4               | 14                | 14           | 13            | 3        | 4                        | 7              | 6              | 7               |

Each \* denotes a case under 10 years of age

TABLE 10 AN ANALYSIS OF 150 NONDIABETICS ACCORDING TO AGE GROUPS AND AVERAGE SIZE OF ISLETS IN P.U.

| Av Size of Islet, P.U. | Age Groups in Years |     |     |       |       |       |       |       |       |     | Total | %   |
|------------------------|---------------------|-----|-----|-------|-------|-------|-------|-------|-------|-----|-------|-----|
|                        | 0-1                 | 1-3 | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70+ |       |     |
| 0.10-0.19              | 0                   | 0   | 0   | 0     | 0     | 0     | 0     | 0     | 0     | 0   | 0     | 0   |
| 0.20-0.29              | 10                  | 2   | 12  | 0     | 2     | 1     | 1     | 2     | 1     | 0   | 19    | 13  |
| 0.30-0.39              | 7                   | 2   | 14  | 3     | 2     | 1     | 8     | 8     | 2     | 0   | 39    | 26  |
| 0.40-0.49              | 3                   | 0   | 3   | 3     | 1     | 3     | 8     | 8     | 6     | 0   | 32    | 21  |
| 0.50-0.59              | 1                   | 0   | 1   | 3     | 6     | 2     | 4     | 8     | 7     | 3   | 34    | 22  |
| 0.60-0.69              | 0                   | 0   | 0   | 0     | 1     | 2     | 2     | 1     | 4     | 0   | 11    |     |
| 0.70-0.79              | 0                   | 0   | 0   | 0     | 0     | 1     | 3     | 3     | 0     | 0   | 7     |     |
| 0.80-0.89              | 0                   | 0   | 0   | 0     | 1     | 1     | 2     | 0     | 1     | 0   | 5     |     |
| 0.90-0.99              | 0                   | 0   | 0   | 1     | 2     | 0     | 1     | 0     | 0     | 0   | 4     |     |
| 1.0+                   | 0                   | 0   | 0   | 0     | 0     | 0     | 0     | 1     | 0     | 0   | 1     |     |
| Totals                 | 21                  | 4   | 30  | 10    | 15    | 11    | 29    | 31    | 21    | 3   | 150   | 100 |



TABLE 11. ANALYSIS OF 47 DIABETICS ACCORDING TO AGE GROUPS AND AVERAGE SIZE OF ISLETS IN P.U.

| Size of Islet, P.U. | Age Groups in Years |       |       |       |       |       |       |     | Total | %   |
|---------------------|---------------------|-------|-------|-------|-------|-------|-------|-----|-------|-----|
|                     | 0-9                 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70+ |       |     |
| 1-1.19              | 0                   | 0     | 0     | 1     | 0     | 0     | 1     | 1   | 3     | 6   |
| 2-2.29              | 1                   | 0     | 3     | 3     | 0     | 0     | 1     | 0   | 8     | 17  |
| 3-3.39              | 0                   | 0     | 1     | 1     | 1     | 2     | 2     | 1   | 8     | 17  |
| 4-4.49              | 0                   | 0     | 4     | 1     | 1     | 1     | 0     | 0   | 7     | 15  |
| 5-5.59              | 0                   | 0     | 3     | 0     | 3     | 3     | 2     | 1   | 12    | 26  |
| 6-6.69              | 0                   | 0     | 1     | 1     | 0     | 1     | 2     | 0   | 5     | 11  |
| 7-7.79              | 0                   | 0     | 0     | 0     | 1     | 0     | 0     | 0   | 1     | 2   |
| 8-8.89              | 0                   | 0     | 0     | 0     | 0     | 1     | 1     | 0   | 2     | 4   |
| 9-9.99              | 0                   | 0     | 0     | 0     | 0     | 0     | 1     | 0   | 1     | 2   |
| Totals              | 1                   | 0     | 12    | 7     | 6     | 8     | 10    | 3   | 47    | 100 |

the enlarged islets occur chiefly in cases over 50 years of age, in contrast with the nondiabetics among whom enlarged islets occur in all adult age groups.

It is clear, then, that in diabetes mellitus the reduction in the amount of islet tissue is largely the result of a reduction in the number of islets.

Malignant disease (14 cases); tuberculosis (14 cases); blood diseases (13 cases); syphilis (3 cases). Of the total of 44 cases making up the above disease groups, 26 (59%) had over 50 islets in 10 microscopic fields, a frequency about 4 times as great as in acute diseases (table 9). The 4 cases under 10 years of age each had over 80 islets in 10 fields.

The size of the average islets was over 0.6 P.U. in 3 of the 44 cases (25.5%, table 12) as compared with 6.7 per cent in acute diseases (table 10). All cases under 10 years of age had average islets under 0.6 P.U. in size.

TABLE 12. ANALYSIS OF A NUMBER OF DISEASE GROUPS AND ISLET AREA GROUPS ACCORDING TO AVERAGE SIZE OF ISLETS IN P.U.

| Av. Size of Islets, P.U. | Acute diseases | Aplastic anemia | Malignant disease | Tuberculosis | Blood diseases | Syphilis | Nondiabetics under 0.9% | 3.6 to 4.6% | 4.6 to 5.5% | over 5.5% |
|--------------------------|----------------|-----------------|-------------------|--------------|----------------|----------|-------------------------|-------------|-------------|-----------|
| 0.1-0.19                 | 0              | 0               | 0                 | 0            | 0              | 0        | 0                       | 0           | 0           | 0         |
| 0.2-0.29                 | 2*             | 0               | 0                 | 0            | 0              | 0        | 2                       | 1*          | 0           | 1*        |
| 0.3-0.39                 | 7*             | 1               | 3                 | 4**          | 2*             | 2        | 2                       | 2*          | 0           | 1*        |
| 0.4-0.49                 | 5              | 1               | 2*                | 4            | 1              | 0        | 0                       | 0           | 2*          | 3*        |
| 0.5-0.59                 | 5              | 0               | 5                 | 4            | 4              | 0        | 0                       | 1           | 0           | 0         |
| 0.6-0.69                 | 1              | 1               | 2                 | 1            | 3              | 0        | 0                       | 3           | 0           | 0         |
| 0.7-0.79                 | 1              | 0               | 1                 | 0            | 2              | 0        | 0                       | 0           | 0           | 1         |
| 0.8-0.89                 | 1              | 1               | 0                 | 0            | 1              | 0        | 0                       | 0           | 1           | 1         |
| 0.9-0.99                 | 1              | 0               | 0                 | 1            | 0              | 0        | 0                       | 0           | 2           | 0         |
| 1.0+over                 | 0              | 0               | 1                 | 0            | 0              | 0        | 0                       | 0           | 1           | 0         |
| Totals                   | 23             | 4               | 14                | 14           | 13             | 3        | 4                       | 7           | 6           | 7         |

Each \* denotes a case under 10 years of age

The indications are, therefore, that the increased islet tissue content in these disease groups is due to an increase both in the number and in the size of the islets. Those under 10 years of age (4 cases) had numerous islets which were within the normal limits as to size.

### Cases with Islet Area Readings per Field of 3.6 per cent and Over

All but one of these 20 cases had islet counts of over 50 to 100 microscopic fields, while the 6 cases under 10 years of age had over 100 islets each (table 9). The average size in 9 cases (45%) was over 0.6 P.U. (table 12); the remaining 11 cases, including 6 under 10 years of age, were under 0.6 P.U.

TABLE 13. NUMBER AND SIZE OF ISLETS IN VARIOUS GROUPS

| Group   | No. of Islets in 10 Fields                     | Size of Average Islets, P.U. |
|---|--|------------------------------|
| Nondiabetics under 10 years                               | 50 and over                                    | 0.2 to 0.4<br>none > 0.6     |
| Nondiabetics over 10 years                                | 20 to 50<br>(30% in higher groups)             | 0.3 to 0.6<br>(19% > 0.6)    |
| Acute diseases  | 20 to 50                                       | 0.3 to 0.6                   |
| Diabetes mellitus   | 10 to 30                                       | 0.1 to 0.6                   |
| Malignant disease, tuberculosis, blood diseases, syphilis | 20 to 50, 41%<br>over 50, 49%                  | 0.3 to 0.6                   |
| Cases with islet area readings of 3.6% and over           | a) over 10 yr., > 50<br>b) under 10 yr., > 100 | a) > 0.6<br>b) < 0.6         |

These results show that the higher islet area readings are generally associated with an increased number of islets, especially in children under 10 years of age. In adults, however, the increase may be due to enlarged islets. On the whole, therefore, children have a greater number of islets than adults but the average size is less.

The data resulting from the various analyses of the cases according to the number and the size of the islets are summarized in table 13.

### DISCUSSION

The main problems connected with this investigation are a), those concerned with the establishment of normal standards, and b), those associated with the changes in the islet tissue content in disease. The work of Ogilvie has a direct bearing on the points raised under the first heading, while the data available for the second section are provided by the present series.

*Normal standards* Ogilvie, in his series, had apparently selected his cases to cover the whole age range, he did not consider the possibility of any alteration in the islet tissue content as the result of disease. Since the present series is essentially of an unselected character, the results lend themselves both to age and sex analyses as well as to the study of any reaction the islet tissue content may have to disease.

TABLE 14 OGILVIE'S SERIES ON ISLET AREA IN PANCREATIC TISSUE

| Islet area groups, % | Age Groups in Years |    |   |               |     |       |       |       |       |       |       | Total |
|----------------------|---------------------|----|---|---------------|-----|-------|-------|-------|-------|-------|-------|-------|
|                      | Under 1             | 1  | 2 | Total under 3 | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 |       |
| under 9              | 0                   | 0  | 0 | 0             | 0   | 0     | 1     | 0     | 3     | 0     | 0     | 4     |
| 9-17                 | 0                   | 0  | 1 | 1             | 4   | 12    | 7     | 3     | 1     | 4     | 2     | 33    |
| 18-26                | 5                   | 2  | 0 | 7             | 11  | 5     | 3     | 1     | 5     | 2     | 0     | 27    |
| 27-35                | 6                   | 7  | 2 | 15            | 15  | 1     | 1     | 0     | 0     | 1     | 0     | 18    |
| 36-45                | 5                   | 0  | 0 | 5             | 6   | 0     | 0     | 0     | 0     | 0     | 0     | 6     |
| 46-55                | 7                   | 2  | 1 | 10            | 10  | 0     | 0     | 0     | 0     | 0     | 0     | 10    |
| over 55              | 1                   | 1  | 0 | 2             | 2   | 0     | 0     | 0     | 0     | 0     | 0     | 2     |
| Total                | 24                  | 12 | 4 | 40            | 48  | 18    | 12    | 4     | 9     | 7     | 2     | 100   |

Both series are subjected to similar analyses in tables 14 and 15. Ogilvie's results have been converted into percentage readings in order to make a direct comparison possible.

If the 0.9 per cent group can be excluded as diabetics and potential diabetics, then the 0.9, 1.8 and 2.7 per cent groups include the greater part of both series, i.e. 74.5 per cent of the present series (table 15) and 78 per cent of the Ogilvie series (table 14). Those groups constitute the normal range previously referred to. In both series, too, the figures for these groups correspond both individually and collectively.

Among the infants the Ogilvie series shows quite definitely that there is a tendency for the islet area

readings to be higher than in adults. In his complete series including both infants and adults there were 36 cases with readings of 2.6 per cent and over. Of these, 32 were infants and this was four-fifths of the total number of infant cases in the series. Furthermore, among the still higher readings the infant predominance is even more striking. Of the 18 cases over 3.6 per cent only one was not an infant and this one was under 10 years of age.

In the present series the higher readings (over 3.6%) occur to a great extent among the infants under 3, and then with decreasing incidence up to 20 years of age. This corresponds with the findings in Ogilvie's series although in his cases the proportion of higher readings was greater. A further difference in the findings of the two investigations is that although the higher readings in Ogilvie's series are restricted to the infant group, similar readings were found in the present series in 12 cases over 40 years of age or 6 per cent of the whole series. Thus the figures indicate that a high islet tissue content may be a), of congenital origin, which as a rule disappears by 20 years of age, or b), of an adult type which makes its appearance after 40 years of age.

Ogilvie's data lead him to conclude that during the first year of life the amount of islet tissue is augmented by an increase in the number of islets, then hyperplasia sets in, and by the third year both processes are at work at about the same rate. During childhood and adolescence any increase in the amount of islet tissue is through hypertrophy. At 21 years of age the islet tissue content has become established. These conclusions of Ogilvie conform with the findings of the present investigation.

However, the high islet tissue content in cases over 40 years of age has still to be explained. This was not a feature of Ogilvie's cases but did occur quite definitely in the present series and will be considered at a later stage in this report.

*Variations of islet tissue content due to disease.*

TABLE 15 ISLET AREA IN PANCREAS IN PRESENT SERIES

| Islet Area Groups % | Age Groups in Years |   |   |               |     |       |       |       |       |       |       |     |              |                     | Totals |
|---------------------|---------------------|---|---|---------------|-----|-------|-------|-------|-------|-------|-------|-----|--------------|---------------------|--------|
|                     | Under 1             | 1 | 2 | Total under 3 | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70+ | Age un known | Age or sex un known |        |
| under 0.9           | 0                   | 0 | 0 | 0             | 1   | 0     | 9     | 6     | 2     | 5     | 5     | 3   | 0            | 2                   | 33     |
| 0.9-1.7             | 7                   | 2 | 0 | 9             | 11  | 5     | 7     | 7     | 12    | 18    | 8     | 1   | 0            | 2                   | 71     |
| 1.8-2.6             | 7                   | 0 | 0 | 7             | 7   | 2     | 8     | 3     | 10    | 7     | 14    | 1   | 1            | 0                   | 53     |
| 2.7-3.5             | 3                   | 1 | 0 | 4             | 6   | 1     | 3     | 2     | 6     | 5     | 1     | 1   | 0            | 0                   | 25     |
| 3.6-4.5             | 1                   | 0 | 0 | 1             | 2   | 1     | 0     | 0     | 1     | 2     | 1     | 0   | 0            | 0                   | 7      |
| 4.6-5.5             | 1                   | 0 | 0 | 1             | 1   | 1     | 0     | 0     | 2     | 1     | 1     | 0   | 0            | 0                   | 6      |
| over 5.5            | 2                   | 1 | 0 | 3             | 3   | 0     | 0     | 0     | 2     | 1     | 1     | 0   | 0            | 0                   | 7      |
| Totals              | 21                  | 4 | 0 | 25            | 31  | 10    | 27    | 18    | 35    | 39    | 31    | 6   | 1            | 4                   | 202    |

Diabetes mellitus in all of its phases is too familiar to require any discussion here. However, hypoglycemia or hyperinsulinism is not so well known and hence a summary of the literature on this condition may be of assistance. The subject has been reviewed by Gammon and Tenery (3), and Wauchope (4).

Harris (5) examined the fasting blood sugar in 1,497 cases and found 67 in whom the level was 0.079 per

The age and sex incidence of hypoglycemia also has its interesting features. The 30 to 50-year-age groups are most affected but the condition may appear at any age. It is reported to be twice as common in men.

In children hypoglycemia also is a problem. Wauchope (4) found the blood sugar in those under 3 years of age lower than in adults. According to Harris

DETAILS OF CASES ILLUSTRATED IN DIAGRAMS (FIG. 1 TO 21)

| Fig. | Case | Sex and age | Disease  | Islet area % | No. of islets in 10 fields | Remarks                                      |
|------|------|-------------|--|--------------|----------------------------|--|
| 1    | 16   | M, 43       | Acute pericarditis   | 1.3          | 40                         | Normal                                       |
| 2    | 37   | M, 59       | Dislocated vertebrae   | 1.8          | 53                         |  |
| 3    | 386  | M, 58       | Adrenal atrophy<br>Acute pericarditis  | 0.7          | 22                         | Nondiabetic with reading under 0.9%          |
| 4    | 205  | F, 7        | Chloroma   | 3.7          | 131                        | Nondiabetics with readings of 3.6 to 4.6%    |
| 5    | 28   | M, 66       | Pulmonary tuberculosis   | 4.4          | 71                         |  |
| 6    | 188  | M, 6 mo.    | Lymphosarcoma, bronchopneumonia, Otitis media, cerebral abscess, pyemia<br>Tuberc. spine, tuberc. bronchopneumonia | 4.7          | 119                        | Nondiabetics with readings of 4.6 to 5.5%    |
| 7    | 211  | F, 43       |  | 4.9          | 61                         |  |
| 8    | 31   | M, 12       |  | 5.2          | 140                        |  |
| 9    | 91   | M, 56       | Pellagra, carcinoma of tongue<br>Cerebrospinal meningitis  | 7.8          | 123                        | Nondiabetics with readings of 5.5% and over  |
| 10   | 329  | M, 3 mo.    |  | 5.5          | 135                        |  |
| 11   | 256  | F, 24       | Diabetes mellitus  | 0.7          | 18                         | Diabetics with readings under 0.9%           |
| 12   | 364  | M, 63       | Diabetes mellitus  | 0.8          | 18                         |  |
| 13   | 365  | M, 55       | Diabetes mellitus, coronary atheroma   | 0.6          | 13                         |  |
| 14   | 224  | F, 73       | Diabetes mellitus, ulcerative colitis  | 0.5          | 10                         |  |
| 15   | 5    |             | Diabetes mellitus  | 0.2          | 22                         |  |
| 16   | 29   | M, 65       | Hemochromatosis  | 0.2          | 10                         |  |
| 17   | 237  | F, 54       | Diabetes mellitus  | 1.6          | 21                         | Diabetics with readings between 0.9 and 1.8% |
| 18   | 378  | F, 54       | Diabetes mellitus, chronic gastric ulcer   | 1.0          | 36                         |  |
| 19   | 142  | M, 49       | Diabetes mellitus  | 0.9          | 32                         |  |
| 20   | 376  | M, 62       | Diabetes mellitus, pyemia, chronic Pb poisoning,   | 4.6          | 55                         | Diabetics with readings of 1.8% and over     |
| 21   | 299  | F, 57       | Diabetes mellitus  | 2.9          | 48                         |  |

cent or under. Most of these patients, especially those with blood sugar below 0.069 per cent had symptoms attributable to hypoglycemia. As a result of this study he concluded that mild hypoglycemia was not rare. Later he found among 2541 nondiabetics 218 with various degrees of hypoglycemia including 86 with unmistakable symptoms of the condition (6). The experience of Sippe and Bostock (7) was that in a mixed series of cases the proportion showing hypoglycemia was 0.47 per cent. In the same series there were 0.51 per cent of diabetics. They concluded that hypoglycemia was as common as hyperglycemia.

Diabetics may develop hypoglycemia at a late stage, and this may appear in cases that have not received insulin treatment as well as in those that have. This has been reported by Jonas (8), Joslin (9) and Ashe et al. (10). Hypoglycemia in this form has been termed dyinsulinism.

(6) newly born infants of diabetic mothers may die of hypoglycemia; in such cases the pancreas apparently had been overactive in order to compensate for the lack of insulin in the mother. In consequence, the infant at birth develops hypoglycemia. But hypoglycemia may also occur in infants born of nondiabetic mothers (11).

Little can be said concerning the pathology of hyperinsulinism except that numerous workers have reported the presence of hypertrophy and hyperplasia, and, in some cases, adenomata of the islet tissue, while in a few cases the causal lesion was a carcinoma of islet origin.

It is evident, therefore, that conditions exist in which structural features in the islets correspond, on the one hand, with underactivity (hypoinsulinism), and, on the other hand, with overactivity (hyperinsulinism); these conditions can be determined to a large extent by ascertaining the proportion of the

islet tissue present. Although this series contains a group of diabetics to illustrate underactivity of islet tissue it does not include any authenticated cases of hyperinsulinism. However, the readings at the upper extreme are sufficiently high to suggest an islet tissue content greater than the normal. A low islet tissue content occurred in very few nondiabetics of both series. Ogilvie in his series of 100 normal cases had only 4 in the 0.9 per cent group. In the present series

The diagrams for the group of acute cases (fig. 1 and 2) serve as normals. In them there is as a rule a general increase in the height of the columns, although in a few instances the rise tends to be rather sharp. In general the appearances seem to be analogous to those in a normal incidence curve.

An examination of the bar diagrams of the diabetic group with readings under 0.9 per cent discloses that there are three types. A) There are those in

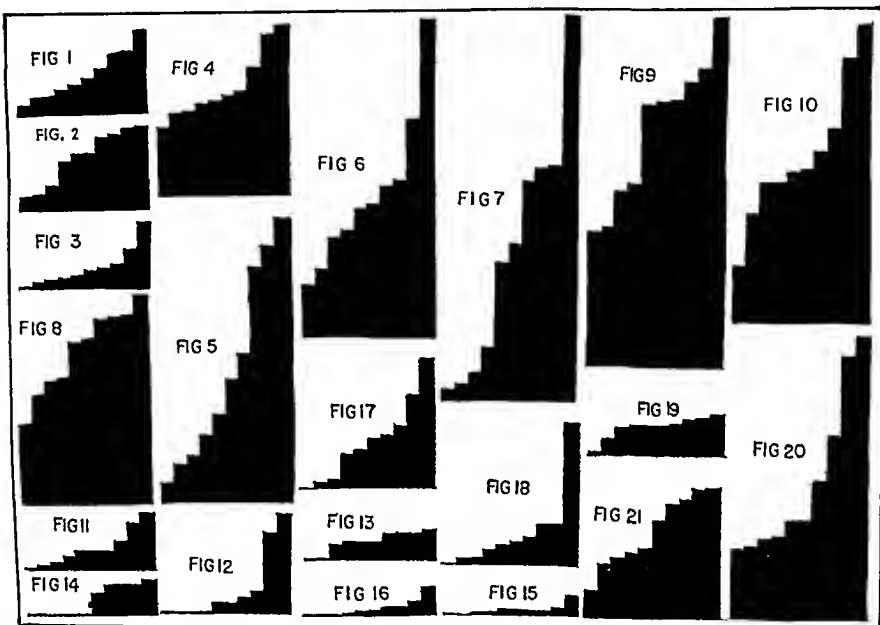


FIG 1-10. BAR DIAGRAMS OF GENERAL GROUP READINGS OF ISLET TISSUE. Each figure represents 10 fields (abscissae); the ordinate values represent 0.5 planimeter units converted readings less than 0.9%, fig. 4 and 5, readings from 3.6 to 4.6%, fig. 6-8, readings 4.6

FIG 11-21. BAR DIAGRAMS OF DIABETIC GROUP READINGS, see legend for fig. 1-10. FIG 0.9 to 1.8%, fig. 20-21, readings over 1.8%.

a similar group was made up of 29 diabetics and 4 nondiabetics, which appears to confirm the view that an islet tissue content of less than 1 per cent is below normal and is significant of diabetes mellitus.

As the diabetic group contained 22 cases with readings over 0.9 per cent, the complete picture is more complicated than is implied by a low islet reading alone, in consequence the group requires further study. At this stage bar diagrams were found to be a useful form of analysis.

The bar diagrams were made by plotting the 10 individual readings for each case (abscissae) against planimeter units as the vertical measure (ordinates)

which all the columns are very low (fig. 13-16) implying low readings throughout and therefore extensive and uniform islet damage. B) There are those in which low columns are associated with one or several peaks (fig. 12). In these cases islet damage had been followed by some measure of repair either by an increase in the number or the size of the islets, which in turn has given rise to the higher reading. C) There are those which show a reduced normal diagram indicating a uniform reduction of the islet tissue best explained by the assumption of a generalized islet atrophy (fig. 11). In brief, then, the above types represent cases in which there had been extensive

islet tissue damage with or without repair of a compensatory type, and a separate group in which the low islet tissue content was due to uniform islet atrophy.

In the diabetic group of 0.9 to 1.8 per cent the bar diagrams are mostly of the normal type (fig. 17). A number, however, show the steep upward trend suggestive of compensatory repair (fig. 18). In some the diagrams are in the form of a plateau (fig. 19); this could be explained by the assumption that regeneration had occurred throughout. Those cases in the diabetic group with readings over 1.8 per cent, had exaggerated normal diagrams suggestive of a general hypertrophy or hyperplasia of islet tissue (fig. 20 and 21).

But it must not be lost sight of that many of the diabetics with readings over 0.9 per cent show some degree of hydropic or hyalin degeneration of the islets; such areas cannot be excluded in making the area measurements as they frequently occur in scattered patches within the islets. It is clear therefore that a mere increase in the islet area cannot be the sole criterion of the effectiveness of that islet.

The 4 nondiabetics with readings under 0.9 per cent had bar diagrams which were of the miniature normal type and similar to a form seen among the diabetics (fig. 3); this was assumed to be significant of a uniform atrophy of the islets.

The groups with high islet tissue content have still to be considered. Table 5 shows that the higher readings occurred chiefly in males (males 15; females 5), and in addition to infants, adults over 40 years had a high incidence. This is in accordance with the clinical experience of hypoglycemia. The bar diagrams of all groups with readings over 3.6 per cent, with the exception of 3 cases, show an exaggerated normal appearance (fig. 4-10), and therefore represent either hypertrophy or hyperplasia of the islets in general, or an increased number of islets, rather than compensatory repair following islet damage.

In this series there were no authenticated cases of hypoglycemia but any of the 20 cases with readings over 3.6 per cent might have been potential or pos-

sibly actual cases of hypoglycemia, especially since various workers have found that hypoglycemia is as common as hyperglycemia or diabetes mellitus.

#### CONCLUSIONS

In sections of the pancreas in 202 cases including 51 diabetics, the islets in each of 10 microscopic fields were drawn by a camera lucida, and their total islet area was estimated by a planimeter. The results, in percentage of islet to pancreatic tissue, were analyzed to find out if age, sex, or disease were associated with variations in the total islet tissue content, or in the size or number of islets.

At the one extreme are cases with low islet tissue content and these are almost exclusively diabetics. At the other extreme are those with a high proportion of islet tissue, and the latter were principally infants, or adults with chronic or proliferative diseases.

Under 0.9 per cent of islet tissue is presumably significant of a deficiency of insulin secretion since it occurs in the great majority of cases of diabetes mellitus.

From 0.9 to 2.7 per cent may be considered normal for adults, and from 0.9 to 3.6 per cent normal for infants.

Over 3.6 per cent is classed as high and probably significant of potential or actual hypoglycemia.

I am grateful to Professor Baker for his interest and helpful criticism.

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# Clinical Studies with Male Hormone

## V. Therapeutic Use of Pellets of Testosterone Propionate

### [Pellet Implantation]

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ADMINISTRATION OF HORMONES by the implantation of compressed pellets of the pure substances has been practiced extensively since the introduction of this technique by Deanesly in 1937 (1). Pellets of desoxycorticosterone acetate have been carefully studied by Thorn and his collaborators, and their therapeutic usefulness in patients suffering from Addison's disease has been established (2, 3, 4).

Although the experimental use of androgenic steroids in patients was begun even before desoxycorticosterone was available, the therapeutic use of pellets of testosterone derivatives in patients suffering with androgen deficiency is by no means established on a sure foundation. For this delay there are several reasons.

There has not yet been evolved any standardization of dosage of androgenic substances in any of the techniques of administration. The criteria of adequate and optimal therapeutic effect are matters on which workers in this field have not reached a uniformity of opinion (5, 6). One great difficulty lies in the fact that the metabolic responses to androgenic compounds cannot be measured quantitatively as well as the response to adrenal cortical compounds, and accordingly one must depend on clinical (and often subjective) signs which cannot be assayed accurately.

Pellets of androgenic compounds made by hand lack uniformity in size and consistency, and have given discordant results in the hands of different investigators (vide infra). Androgenic pellets also have a greater tendency to slough than do pellets of desoxycorticosterone compounds, probably due to a more vigorous foreign body reaction (5, 6, 7). It perhaps should be reemphasized that in no instance have we found infection to play a rôle in sloughing the pellets.

It has been difficult to find patients willing to return at frequent intervals for surgical removal of pellets, so that they may be weighed and the rate of absorption of the material determined. Many of the patients live considerable distances from Baltimore.

and most of them are regularly employed. Furthermore, the search for the pellets several months after implantation is not always easy, and the probing required to find them is sometimes associated with considerable pain. Often in the surgical removal of pellets for assay, small pieces of the pellets are chipped off, thus rendering them valueless for weight assay.

The absorption curves for pellets of androgens have been studied rather extensively in animals. Most of the reports, however, are concerned with small pellets weighing only 10 mg. or less. Forbes (9) reviewed the literature on the subject and reported his own extensive experiments on the absorption rate of small pellets in the rat. He found that small pellets of testosterone, methyl testosterone and testosterone monopropionate were absorbed on a linear curve (this curve showed the percentage loss per day of each pellet), and he concluded that "such pellets should supply roughly (although not exactly) the same amount of hormone daily until the pellet is about 90% absorbed." Vest, Drew, and Langworthy (10) implanted considerably larger pellets (weighing 300-350 mg. each) in macaques and removed them later for assay. All of the workers with androgen implants in animals have agreed that a) the absorption rate probably varies with the surface area of the pellet rather than with its weight, b) that the density of the pellet is an important factor in the absorption rate, and c) that testosterone, methyl testosterone, testosterone monopropionate and testosterone dipropionate are absorbed in descending order of rapidity.

Only a few reports on the use of androgen pellets in man have come to our attention. In 1939 Howard and Vest (8) reported the successful use of large pellets of testosterone in hypogonad patients. The same authors in the same year also reported successful pellet implantations with the use of an 'injector' instrument (7). Biskind, Escamilla and Lissner (11) implanted many small pellets of methyl testosterone in a series of hypogonad patients. Their pellets varied from 80 to 180 mg. Judged by the subjective effect, these pellets were therapeutically satisfactory for periods of 33

TABLE 1. ABSORPTION RATE FROM TESTOSTERONE PROPIONATE PELLETS IMPLANTED IN THE INFRASCAPULAR REGION

| Patient | Implanta-<br>tion Date | Removal<br>Date                          | Weights                     | Days                | Average<br>per Day                  |
|---------|------------------------|--|-----------------------------|---------------------|-------------------------------------|
| W.E.P.  | 5/17/40                | 3/12/41                                  | mg.<br>63<br>29<br>20<br>40 | 300                 | mg.<br>0.46<br>0.57<br>0.60<br>0.53 |
| B. R.   | 7/19/40                | 1/ 8/41                                  | 42<br>48                    | 174                 | 0.91<br>0.87                        |
| S. J.   | 6/10/40                | 9/27/40                                  | 90                          | 109                 | 1.00                                |
| I. W.   | 4/10/40                | 11/14/40                                 | 50                          | 218                 | 0.70                                |
| D. M.   | 10/ 5/40               | 4/ 8/41                                  | 70<br>93<br>90<br>65        | 185                 | 0.70<br>0.58<br>0.59<br>0.73        |
| J. H.   | 6/ 2/41                | 9/ 9/41                                  | 120                         | 99                  | 0.83                                |
| S. J.   | 9/27/40                | 4/16/41                                  | 70                          | 201                 | 0.65                                |
| W. G.   | 9/25/40                | *  | 134<br>114<br>117           | 77<br>127<br>137    | 0.85<br>0.68<br>0.60                |
| J. R.   | 4/10/40                | 2/ 1/41                                  | 56                          | 296                 | 0.50                                |
| R. E.   | 5/ 1/40                | 6/13/41                                  | 35<br>38<br>39<br>26        | 408 <sup>1</sup>    | 0.40<br>0.40<br>0.40<br>0.43        |
| W. A.   | 5/ 1/40                | 6/18/41                                  | 12                          | 413 <sup>1</sup>    | 0.46                                |
| R. H.   | 7/17/40                | 11/ 6/40                                 | 107<br>97<br>110<br>110     | 112 <sup>2</sup>    | 0.83<br>0.92<br>0.80<br>0.80        |
| B. H.   | 9/ 3/41                | 9/11/41<br>9/17/41<br>9/24/41<br>9/30/41 | 181<br>179<br>175<br>172    | 8<br>14<br>21<br>27 | 2.40<br>1.50<br>1.19<br>1.03        |
| R. C.   | 9/18/41                | 9/25/41<br>10/ 2/41<br>10/ 9/41          | 178<br>183<br>174           | 7<br>14<br>21       | 3.10<br>1.18<br>1.25                |
| A. S.   | 12/13/40               | 10/17/41                                 | 35                          | 307                 | 0.50                                |

<sup>1</sup> Subjectively, therapy considered inadequate for 3 months.

<sup>2</sup> Subjectively, therapy considered inadequate for 2 weeks.

\* Sloughed on 12/11/40, 1/30/41 and 2/9/41.

to 79 days. Dorfman and Hamilton (12) implanted pellets of 10 mg. each on two occasions, once the total dosage being 90 mg. and again 280 mg. There was not entirely satisfactory clinical response (subjective) in either case. In a very recent paper Escamilla and Lissner (13) reported on the clinical use of larger pellets each weighing 200 mg. In one patient 4 pellets of methyl testosterone totaling 800 mg. proved subjectively adequate for 3½ months. The pellets were removed after 4 months and had lost per day an average of 3.5 mg. or not quite 0.87 per pellet per day. In another

case 3 pellets of methyl testosterone were implanted and proved effective for only 11 weeks. In the third case in which they used 200 mg. pellets, 800 mg. was implanted. The patient was lost sight of two months later at which time the implantation seemed to be subjectively adequate.

#### METHODS

The primary object of this article is to report observations on the absorption of pellets of testosterone propionate. All pellets used in this series were machine-made under uniform aseptic conditions and they weighed approximately 200 mg.<sup>1</sup> Because of the possibility of bacterial contamination we have not weighed the pellets prior to implantation. Ten pellets, however, were picked at random by the manufacturers from a large lot and their weights were found to vary from 207.8 to 200.2 mg. The mean weight of these ten pellets was 202.6 mg., and the average deviation from the mean was 1.8 mg. All the pellets were implanted by essentially the same technic as reported previously from this clinic (8) except that the sites in all instances were in the infrascapular region upon the muscle fascia, and each pellet was placed at a distance of approximately 6 cm. from the incision line. A small pocket was made for each pellet by inserting a closed Halsted clamp backward along the fascia from the incision line and then opening the clamp. Into the pocket thus made one pellet was inserted through a nasal speculum, the opening being closed with a single silk suture.

In evaluating the absorption rates of the pellets only those pellets which were removed entirely intact and unchipped are charted. Because of the technical difficulties previously mentioned, it was possible to gain information of use in absorption rates from only 14 of a total series of 22 implantations which were made with this type of pellet.

#### RESULTS

**Absorption curves.** The data on the rate of absorption of the surgically removed pellets and those which sloughed are shown in table 1. Since it was felt that the absorption rate from pellets which sloughed might not be the same as if they had remained in situ, the data were not at first included in the charts. Their absorption rate falls closely along the general curve of those pellets surgically removed so it was thought permissible to include them in the series. Figure 1 shows the average loss per day from each pellet plotted against the number of days that the pellet remained in situ.

In the earlier cases the pellets were removed only after prolonged periods of time. It was found that, as

<sup>1</sup> These pellets of testosterone propionate (Perandren) were furnished to us by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

a rule, the longer the pellet had remained the less had been its daily loss. Thus it may be seen that in those instances in which the pellets remained more than 400 days after implantation, the average daily absorption amounted to somewhat less than 0.5 mg per day for each pellet. In those instances in which the pellets were removed between 180 and 220 days after implantation, the average daily absorption was between 0.6 and 0.75 mg. Because it had been our impression that the thick fibrous capsule which forms around the pellet was largely responsible for the surprising uniformity of the absorption rate, it seemed likely that the rate would be more rapid in the early days after implantation before the capsule had been formed. In two patients it was possible to remove pellets at weekly intervals after implantation. This hypothesis for absorption of pellet material was found to be correct. It can be seen in the figures that in the first week after implantation there was a rapid loss of the pellet's substance with average daily losses far greater than those found later. Furthermore, the variation in absorption rates in these early days is seen to be greater than at later periods. The initial pellet weights are recorded as 200 mg. Since this may vary between 200 and 208 mg, a considerable error is introduced into the calculation of the first week's absorption rate. Since all pellets weighed more than 200 mg, the proportional difference between absorption rate between the first week and succeeding weeks would be even greater than that shown in the figures. A greater variation in absorption rate might be anticipated in the first week since one would expect considerable difference in tissue reactivity (and, hence, rate of capsule formation) from patient to patient.

**Therapeutic effectiveness.** The difficulties involved in evaluating the therapeutic effectiveness of androgen administration have been discussed (3). As an aid in this evaluation the most striking objective changes in our first group of hypogonad patients treated with 25 mg of testosterone propionate twice each week were charted. We have termed this chart the primary pattern of response (4). Six of the cases included in this present report had had no androgenic therapy prior to the implantation of the five 200 mg pellets of testosterone propionate. In all of these six cases the objective response fell well within the limit of, or—in many instances—bettered, our primary pattern. Therefore, the androgenic therapy supplied by the pellets was as good as if not better than that produced by the injection of 25 mg of testosterone propionate twice each week.

In the eight patients of this group who previously had been given effective androgenic therapy by some other method, the implantation of five 200 mg pellets maintained or advanced the effects previously obtained.

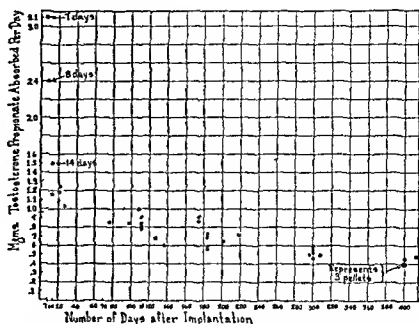


FIG. 1. EACH POINT ON THE GRAPH REPRESENTS THE AMOUNT OF THE DRUG ABSORBED PER DAY FROM AN INDIVIDUAL PELLET. These figures are calculated by subtracting the weight of the pellet at the time of removal from its initial weight, and dividing by the number of days the pellet remained in situ.

**Duration of pellet effects.** We have repeatedly emphasized the dangers of relying on subjective criteria in evaluating androgenic therapy (5, 6, 8). However in estimating the effective duration of the pellets in this series of cases, we are compelled to rely on the patients' own evaluations to a considerable extent. We have found, using other methods of administration, that when effective therapy ceases, the patients complain of certain changes in their status which are fairly characteristic. Among these are a), the failure of ejaculation, b) loss of libido and c), a general deterioration in the sense of well being. These symptoms are reported long before we are able to detect any objective regression except a diminution of the amount of prostatic secretion obtained by massage.

Four patients in this series complained that the pellets had become ineffective or, as they expressed it, had "run out" at the time of their removal. Two of these were those in whom the pellets had remained more than 400 days. Patient W. A. stated that his treatment had not been "good enough" for about two months, in other words, the 5 pellets had given him subjectively satisfactory response for approximately 350 days. In the case of Patient R. E., the feeling was expressed that he had needed "more stuff" for nearly 4 months prior to the date of pellet removal. Thus, subjectively, the pellet had been adequate for about 290 days. Patient A. S. reported at 307 days that the pellets had been "not so good for 7 weeks though they are still working some." Patient R. H. felt that the pellets had yielded adequate therapy for only a little over three months and the reason for his return to us on the 112th day was that "the pellets have run out now for about two weeks." All of the other patients in this series felt that for the duration of their implants the therapeutic effects derived were entirely adequate and satisfactory. One other patient, not in-



cluded in this series because we were unable to remove the pellets for assay, felt that the five 200 mg. pellets were adequate for only four months.

#### INTERPRETATION OF RESULTS AND DISCUSSION

Our interpretation of the above results is as follows. In the first few days after pellet implantation there is a rather rapid absorption amounting to as much as 3 or more milligrams per day from each pellet. After this, presumably with capsule formation, the absorption rate steadies down to a surprisingly constant rate somewhere between 0.5 to 1.0 mg. per day. This daily absorption rate will continue for many days, falling gradually until the pellet has become very small. This is in line with the findings of Forbes in his rat experiments.

Upon many variable factors will depend the amount of androgen required to maintain adequate response in a group of hypogonad patients. It seems unreasonable to suppose that every patient suffering from hypogonadism will require the same daily dose of androgen. Since each pellet in the period between the 15th and the 200th day yields from 0.6 to 0.9 mg. per day, the combined yield of 5 pellets would be between 3 and 4.5 mg. For a patient who requires for adequate subjective effect a minimum of 4 mg. per day 5 pellets would be sufficient for a considerably shorter period of time than would be the case for a patient whose required dosage might be only 3 mg. per day. If this hypothesis is correct, in a patient in whom 5 pellets have become inadequate in 4 or 5 months we should be able to provide an adequate absorption level by implanting 2 more pellets. Then, perhaps, when a new implant is considered, 7 or 8 pellets might be more suitable than 5. It should be stressed that five 200 mg. pellets have been subjectively adequate in all of our patients to date for at least 3 months, and in most patients for longer periods.

From these findings we have concluded that during the first week or so after implantation considerably more androgen is absorbed than is necessary. No harmful results have been noted. It is true in the first week or two of therapy that the previously untreated patients have noted much more vigorous stimulation in the sexual sphere than they have experienced later; nevertheless this same subjective overstimulation has occurred at first in all of our hypogonad patients, with any of the methods of androgen administration we have used. This has been attributed to the hypersensitivity that is commonly seen in endocrine deficiencies to the substance that is lacked.

In this paper we are not concerned with optimal or adequate dosage of androgens. However, it seems from the data presented, that one can readily vary the dosage of testosterone propionate over wide limits as may be desired simply by implanting more or

fewer pellets. Our patients who have been treated by pellets, by injection or by oral androgenic therapy have, with a single exception, preferred pellet administration. Other advantages of pellets over intramuscular injection or oral administration of androgens are the great saving of material and the elimination of nuisance to the patient in having to take injections or tablets.

#### SUMMARY

Our experience with machine-made pellets of testosterone propionate implanted beneath the skin in patients suffering with hypogonadism has been discussed. We have found this method of administration satisfactory; it is the most saving of material and, unless the pellets slough, the least trouble to the patient. Duration of effects is discussed, and charts of absorption rates are given. In some patients a given number of pellets supplies subjectively adequate therapy for only a few months, whereas in others this same dose will be effective for a year or more. We have explained this variation in effect on the theory that the former group of patients requires a higher daily supply for adequate subjective effects than do the latter.

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# The Modifying Influence of the Presence of Testicular Tissue on the Efficacy of Testosterone Pellets in the Treatment of the Eunuchoid Patient

## [[Methyl Testosterone Orally]]

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DIVERSIFIED TYPES of eunuchoid patients were employed in this study in order to learn what influence the presence of testicular tissue had on effective doses of testosterone. Two patients were bilateral cryptorchids, 21 and 33 years of age, in whom no testicular tissue was demonstrable. Two others were 20 and 31 years of age and had undeveloped retractile testes which apparently were either nonfunctioning or which gave evidence of a minimal amount of activity. The fifth patient had had an unilateral orchiectomy performed but was deficient in testicular function. The sixth patient exhibited definite hypogonadism which was associated with a primary gonadotropic pituitary deficiency. Subcutaneous implants of testosterone as a method of treatment in cases of testicular deficiency were introduced experimentally by Deanesly and Parkes (1). Following this, reports of the clinical application of this method of therapy appeared in the literature (2). To be clinically expedient, a mode of therapy should be effective; it should have no undesirable side effects and it is essential that it be reasonably inexpensive and possess ease in administration. In order to determine the best method of fulfilling these criteria, the aforementioned six preadolescent eunuchoid patients were employed in our study. The cryptorchid patients acted as excellent controls for comparison with the patients who possessed some testicular tissue.

### METHOD OF STUDY

The study was divided into a clinical and laboratory evaluation, and attempts were made in all cases to integrate the findings by these two methods of approach.

**Clinical study.** General physical examination, basal metabolic rate determinations and roentgenograms of the hands and wrists for the determination of the bone age were made in all cases. Each patient was given an initial subcutaneous implant of 300 mg. of testosterone.<sup>1</sup> The two cryptorchid patients were given a single subsequent implant at an interval of 6 weeks, and following this were given 80 mg. of methyl testosterone by mouth daily. The other four patients received subcutaneous pellet implantations at intervals of 6 to 8 weeks. No oral testosterone was given to these patients. The objective and subjective changes in the patients were recorded before and during the course of the treatment.

**Laboratory study.** Twenty-four-hour collections of urine were assayed at weekly intervals for three successive weeks preceding the administration of any type of medication. This was done in order to secure an approximate idea of the type of androgenic and estrogenic excretion curves in this type of patient. After the implantation of the testosterone, 24-hour collections of urine were secured at 5 to 7 day intervals for a period of 3 to 8 months. All specimens of urine were assayed for estrogens and for androgens. The latter were determined biologically in accordance with our modification of the chick-comb-weight method (3) and colorimetrically according to the method of Neustadt (4). This was done in order to compare the excretion curves of the biologically active material with the colorimetric measurement of the 17-ketosteroids and to learn whether these curves could

<sup>1</sup> The testosterone pellets and the methyl testosterone that were employed in this study were supplied by the Schering Corporation, Bloomfield, N. J. through the kindness of Dr. Edward Henderson.

indicate the proper dose of testosterone that was to be administered to the patients.

*Technique of implantation.* Originally, flat pellets (disks) were employed for subcutaneous implantation. This was accomplished through an incision in the skin after preliminary infiltration with 2 per cent novocain. A point was chosen between the seventh and ninth ribs in the midaxillary line. The incision was made in the intercostal space and varied from 1 to 3



Fig. 1-3. Patient W. M. Fig. 1. BEFORE TREATMENT. Notice female configuration of body outline. Age 33 yr. Fig. 2. Close-up shows scars of unsuccessful orchipexy. Observe absence of testes. Fig. 3. After receiving 450 mg. testosterone subcutaneously. Marked and rapid response resulted within 2 months.

inches in length. Small pockets were then made in the subcutaneous tissue and a small nasal speculum was introduced into the pockets thus formed. The disks were slipped into the pockets between the separated blades of the speculum. This gave a comparatively dry field and facilitated introduction of the pellet. Following this earlier method of implantation, it was shown that the immediate rate of absorption of the testosterone depended upon the degree of surface contact which the pellet made with the body fluid (5, 6, 7) rather than upon the mass of the pellet. Consequently the use of cylindrical pellets measuring 3 by 8 mm.

was adopted in this work. This type of pellet has since simplified the method of administration. In place of making an incision in the conventional manner, a number 3 trocar with a beveled edge is introduced subcutaneously, after the skin has been infiltrated with 2 per cent novocain. No preliminary nicking of the skin with a scalpel is necessary. Up to 6 or even 8 pellets, each weighing 75 mg., can thus be introduced at one time. No suture is required and a small dry dressing suffices. The advantages of this method of administration immediately become apparent. It is simple, rapid, leaves no scar and facilitates the initial rate of absorption of the testosterone.

#### CASE HISTORIES

*Patient 1, A. C.,* age 21 years had always suffered from bilateral cryptorchidism. The patient exhibited the findings typical of a pre-adolescent eunuchoid. He measured 73 1/2 inches in height, his span was 78 1/8 inches, and his weight was 181 pounds. His face was smooth and he had never shaved; there was an extremely sparse growth of pubic hair; there was no axillary hair nor hair on his chest. The genitals were small, the penis being infantile in size; the scrotum was flat and resembled labial folds; the prostate was small, being about the size of that of a prepuberal boy. His B. M. R. was -16 per cent. Roentgenograms of the hands and wrists showed failure of epiphyseal closure and the bone age was that of a boy of 14 years, 9 months. The patient had never had erections or nocturnal emissions. On 3/1/41, 300 mg. of testosterone was implanted under the skin. Priapism occurred 3 days after implantation of the pellet. At this time there was also an increased output of urine. On 5/17/41, 300 mg. was again inserted. The penis was definitely increased in size, the prostate was larger and pubic and axillary hair showed rapid growth. On 6/14/41, the patient weighed 200 pounds (a gain of 19 pounds), measured 74 1/2 inches (grew 1 1/4 inches), and his span was 81 inches (2 7/8 inches increase). Beginning 6/21/41, the patient was given daily oral doses of 80 mg. of methyl testosterone. The general improvement continued and the patient began to shave once a week on 8/2/41. On 8/30/41 his B. M. R. was +7 per cent. Acne developed on the face for the first time. This is a common finding when the eunuchoids are given androgenic therapy. On 9/20/41 the patient reported that he was shaving three times a week. His height at this time was 75 inches, and his weight was 215 pounds. There was a complete change psychologically; a previously diffident and sensitive individual became an aggressive and self-confident person. The patient informed the authors that he was contemplating marriage in the very near future. Roentgenograms of the hands and wrists which were taken on 9/14/41 showed no progress in epiphyseal closure, the appearance being the same as at the beginning of treatment.

*Patient 2, W. M.,* age 33 years. This patient was similar in all respects to patient A. C. His height was 69 1/2 inches, his span 73 inches, and his weight 202 pounds. He was operated upon on Oct. 17, 1917, for bilateral undescended testes. The testicles were supposed to have been placed in the scrotum, but as far as the patient can recall,

the operation was unsuccessful. Palpation failed to reveal any testicular tissue. The prostate was small and the external genitals were infantile in type. The pubic hair was very sparse, and there was no axillary hair nor hair on the chest. The patient's bone age was that of a boy of 17 years. On 1/27/41, 300 mg of testosterone was implanted subcutaneously. The patient was not seen again until 5/9/41. At this time the penis had definitely increased in size, there was a heavy growth of pubic hair and an increased growth of axillary hair. The patient stated that potency was present for the first time. On 5/13/41, a 150 mg pellet was inserted subcutaneously. A smaller dose than the original was found to be sufficient for the patient's needs. On 6/28/41, the patient began receiving 80 mg of oral methyl testosterone daily. On 8/7/41, a slight acneiform eruption appeared on the face and chest. The patient was then shaving once a week, the prostate was definitely increased in size, and his weight had increased to 213 pounds. His B M R was +26 per cent, pulse 82. The hair growth continued to increase and the genitals reached the biological limits of their growth. The patient has been receiving 60 mg of methyl testosterone daily and up to the present time has shown maintenance of his improved condition.

**Patient 3, A K, age 20.** The patient was first seen on 5/7/37, at which time a diagnosis of cryptorchidism due to primary hypopituitarism was made. His height was 60 1/4 inches and his span was 61 1/4 inches. The B M R was +29 per cent. The glucose tolerance curve showed an increased tolerance for sugar, with the greatest rise being 0.9 per cent. Pregnancy urine extract (200 R U) was given three times a week from 6/5/37 to 11/8/37. His height at this time was 61 1/2 inches, span 62 1/4 inches. Both testicles had descended into the scrotum, but there was no increase in the size of the penis nor scrotum. The prostate was small. Anterior pituitary like substance was then continued for two months more. The patient's physical condition remained static. Roentgenograms taken on 5/5/38 showed retardation in skeletal development. Urinary assays showed the presence of FSH, yet the patient failed to show any improvement in the size of the penis, scrotum or testicles. There was a very slight growth of pubic hair but no axillary hair. The patient was seen again on 3/7/41 after returning from a C C C camp. His height at this time was 66 1/4 inches and his span was 68 1/4 inches. The genital development was unchanged, the testicles were still in the scrotum but they were only pea-sized and were retractile, slipping into the inguinal canals and giving the appearance of undescended testes. On 4/22/41, 300 mg of testosterone propionate was implanted subcutaneously. The patient showed very little improvement. On 5/21/41, 300 mg was again implanted. The scrotum increased in size, the testicles were larger and the penis showed increased growth. The patient was troubled at this time by a mild degree of transient prapism. From this time until 8/7/41, the patient's condition showed no decided improvement. On 8/7/41, 450 mg of testosterone was inserted subcutaneously. On 9/5/41, 300 mg was again inserted subcutaneously. A total of 1350 mg was necessary to bring about improvement in his condition which was comparable to that obtained with 300

mg of testosterone in the cryptorchid cases. The patient's B M R on 9/5/41 was +6 per cent. His height was 67 3/4 inches, weight 128 pounds. This patient developed an acneiform eruption on his face and chest on 9/12/41. His voice became deeper and his skeletal musculature showed increased development.

**Patient 4, J R, age 24 years.** The patient had a bilateral congenital inguinal hernia associated with cryptorchidism. At the age of 12 years, an herniotomy and orchiopexy were done on the right side, the left side was not corrected. Subsequent to this operation, the testicle on the right side



Fig 4-6 Patient A K AGE 20 YEARS Fig 4 BEFORE TREATMENT Small undeveloped testes in scrotum Fig 5 Close up showing undeveloped testes Fig 6 Total of 1350 mg of testosterone required over a period of 5 months to produce effect comparable to those in patient W M

had undergone atrophy. Roentgenograms taken on 9/20/40 and 6/12/41 showed a bone age of 17 years. No progress in epiphyseal closure was observed. The patient was given pregnancy urine extract twice a week for 6 months which resulted in a slight increase in hair growth but no increase in the growth of the genitals. On 10/10/40, the hernia on the left side was corrected and a left orchiopexy was performed. A much atrophied left testicle was brought into the scrotum and fixed. Sufficient testicular activity resulted to bring about improvement in the size of the sex organs and to cause a slight increase in hair growth, but this was not sufficient to cause the patient to shave. On 6/12/41, the patient weighed 139 pounds; his height

was 72 1/4 inches, and his span was 71 1/4 inches. There was definite bilateral gynecomastia. There was no axillary hair and only a moderate growth of pubic hair. The scrotum was fairly well developed. The right testicle was the size of a hazelnut; the left testicle was about the size of a small pea. His B. M. R. was -21 per cent. A pellet of testosterone weighing 150 mg. was implanted under the skin on 6/12/41. The patient stated that enuresis, which had always been present, stopped completely after insertion of the first pellet. We consider this an extremely significant occurrence. As reported by the other patients, there was an increase in the flow of urine during the day. On 7/24/41, 300 mg. of testosterone was inserted under the skin. The gynecomastia began to recede and on 9/6/41 his B. M. R. was -12 per cent; his height was 72 1/2 inches and his weight 135 pounds. The patient's voice was deeper and he exhibited a marked increase in physical endurance.

*Patient 5, J. Y., age 31 years.* Chief complaint was sexual underdevelopment. The patient stated that his testicles were undescended. His family history revealed that his two sisters are hypogonadal and of the eunuchoid type. Examination revealed his height to be 69 inches, span 77 inches, and his weight 144 pounds. The penis was infantile, the scrotum was undeveloped and two small, retractile testes, hazelnut in size, could be forced into the scrotum from the inguinal canals. There was a very slight growth of pubic hair and no axillary hair was visible. The patient had never shaved. On 6/14/41, a roentgenogram of the hands and wrists showed failure of epiphyseal closure. In brief, the patient revealed all of the findings of the typical eunuchoid state. A 300 mg. pellet of testosterone was inserted subcutaneously on 6/14/41. The patient experienced priapism for several days following the insertion of the pellet. Six weeks after the insertion of the pellet, there was an increase in the size of the penis and a slight increase in hair growth. No striking changes were observed. On 7/26/41, 300 mg. of testosterone was again inserted. In the succeeding 6 weeks, the patient showed a moderate degree of general improvement. On 8/30/41, 450 mg. was inserted subcutaneously. At this time his B. M. R. was 0. On 9/4/41, his right knee became swollen and edematous but was painless. On 9/20/41, the edema of the right knee disappeared. Roentgenogram examination of his hands and wrists at this time showed it to be the same as on 6/14/41. His weight was 157 pounds (gain of 13 pounds); height 69 1/4 inches (increase of 1/4 inch). There was a marked increase in axillary and pubic hair. The penis was larger. The skin was a darker tan and ruddier. The patient showed an increase in muscular development.

*Patient 6, C. S., age 31 years.* Patient showed marked obesity, a lack of sexual development, short stature, and failure in facial hair growth. His height was 60 inches; his span was 60 inches, and his weight was 174 pounds. The axillary hair was sparse and there was a slight growth of pubic hair. There were large rolls of abdominal fat and a prominent mons veneris. The penis was infantile, the scrotum was not developed, and the testicles were small, hazelnut in size and retractile. The prostate was prepuberal in type. His B. M. R. was +7 per cent. Roentgeno-

gram examination of the skull showed a sella which was shallow and difficult to visualize. His hands showed complete epiphyseal closure. On 8/12/41, 450 mg. of testosterone was inserted subcutaneously. His primary response was rather delayed, which was similar to that of other patients who had some testicular tissue. On 9/23/41, 300 mg. of testosterone was again inserted subcutaneously. At this time the penis was slightly increased in size and the prostate gland showed a moderate degree of increase.

#### DISCUSSION

From this study it becomes apparent that the presence of testicular tissue, regardless of the amount, will modify the patient's response to the administration of androgenic substance. When there is complete absence of testicular tissue, as in *patients A. C. and W. M.*, the response to treatment is prompt and the amount of material necessary to bring about improvement is minimal. The clinical differences that were observed between these two patients and the four which had a minimal amount of testicular tissue were substantiated in the laboratory by variations in the type of excretion curves that were secured by biological assay as compared to the curves that were secured colorimetrically. This phase of the work is to be discussed in greater detail in a subsequent communication.

It was originally hoped that the excretion curves would be a means whereby the optimum and maintenance doses of testosterone could be determined for each patient, but it was shown in our work that urinary excretion of androgens is no criterion for dosage. This was also suggested by Biskind, et al. (8). It therefore becomes apparent that the clinical response of the patient is the only adequate and practical method for determining the amount of androgenic material to be used and the frequency of its implantation.

The failure of those patients who possessed some testicular tissue to give a maximal early response to the administration of testosterone emphasizes the fact that existing testicular tissue is probably affected by and in turn influences the activity of extraneous androgens. This preparation should not, therefore, be employed in those individuals who do not show a marked anatomical failure in testicular development. This should caution against its promiscuous use. Shay and Gershon-Cohen (9) have shown that testosterone has a depressing influence on the testicles, depending upon the dose that is employed.

We observed that subcutaneous implants of testosterone would stimulate the patient for a period of 6 to 8 weeks. Confirming the observations of Eidelsberg and Ornstein (7), the maximal stimulation occurs during the first month of pellet implantation. This clinical observation is in agreement with the experimental work of Emmens (6) who showed that the rate of ab-

sorption of free testosterone was about 36.8 per cent per month. The second month the total rate of absorption was 87.5 per cent. It was also observed that the initial rate of absorption is greater with cylindrical pellets than with the disk-shaped ones. The latter type of pellet is to be preferred if one wishes to maintain a certain dose level after an initial rapid effect is secured with the cylindrical type. It would therefore appear that a smaller dose of the disk shaped tablet might be used as a maintenance method of treatment.

The choice between the subcutaneous and the oral method must be determined entirely on a clinical basis. We observed that methyl testosterone by the oral route failed to show the excretion of biologically active androgens in the urine. The interpretation of this phenomenon, from our present knowledge, becomes one of academic importance only. Its significance must await more information concerning the intermediary metabolism of the male sex hormone. Clinical response to testosterone is equally good by the subcutaneous and the oral route. The question of expense is the chief objection to the use of methyl testosterone at the present time. The easy administration of the pellets of free testosterone subcutaneously, by means of the trocar, and the comparatively decreased cost strongly recommend it as the method of choice in the treatment of the eunuchoid state.

The disappearance of enuresis in patient 4 (J. R.) lends support to the theory that strengthening of the bladder detrusor musculature is a part of the general skeletal muscular improvement that follows the administration of testosterone. This, according to Kearns (10), may also explain the improved emptying power which follows the use of testosterone in cases of prostatism. Since the depressing influence of testosterone on the testes may be disregarded in cases of prostatism because of the age incidence, it would ap-

pear to be well to recommend its use in selected cases of prostatism.

None of our patients showed any tendency toward epiphyseal closure in the hands and wrists at the end of treatment with testosterone. In the female epiphyseal closure has been said to be linked to the production of estrogen but we have not found the same tendency regarding the supply of androgen in the male.

#### SUMMARY

The presence of testicular tissue in the eunuchoid patient modifies the effectiveness of testosterone. Patients in whom no testicular tissue was demonstrable reacted more readily and required less testosterone than did those in whom some testicular tissue existed. The oral administration of methyl testosterone advanced to the biological limit the anatomical development produced by pellets of subcutaneously implanted testosterone.

Laboratory studies of excretion curves indicate that the clinical response of the patient is the only available criterion for dosage at the present time.

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# Clinical Results Obtained with Sublingual Administration of Methyl Testosterone

## [Menopausal Therapy]

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AFTER RUZICKA (1) and his coworkers in 1935 showed that methyl testosterone was one of the potent substances in a series of twenty compounds evaluated by Tschopp's 10-day cock's comb test, the efficacy of the preparation was also estimated by the seminal vesicle test (2). It was found that, whereas quantities of 50, 100 and 200 micrograms of testosterone produced an increase in weight of the seminal vesicles of 40, 70 and 130 mg. respectively, the same amounts of methyl testosterone produced increases of 50, 114 and 140 mg. respectively. Methyl testosterone was shown by Deanesly and Parkes (3) to be appreciably more active than testosterone on the prostate and seminal vesicles of castrated rats but only one-fifth as active in the capon comb test. It is thus seen that methyl testosterone is the most effective of all of the compounds investigated when evaluated by the seminal vesicle test.

Shapiro (4, 5) showed that methyl testosterone in common with certain other steroids may induce ovulation in *Xenopus laevis*, the South African clawed frog. According to Deanesly (6) methyl testosterone implanted subcutaneously in the form of compressed tablets in castrated rabbits produced striking proliferation and growth of the atrophic uterus masculinus.

According to Miescher and Tschopp (7) the methyl derivative retains its activity much better than testosterone when given by mouth to castrated rats. In their experiments castrated rats were given methyl testosterone dissolved in alcohol by means of a stomach tube in daily doses of 1 and 5 mg. for 10 days; the weight of the seminal vesicle and of the prostate was determined on the 11th day. Of the series of compounds investigated, which included testosterone, 3 c, 17-t-androstanediol, androstenedione, testosterone propionate, androsterone and methyl testosterone, the last named was shown unequivocally to possess the greatest potency on ad-

ministration by mouth. The authors tried to explain this fact by the presence of the methyl group in the 17-position, which is assumed to protect the adjacent hydroxyl group from fermentative processes in the digestive canal and during absorption through the intestinal wall as a result of steric hindrance.

Emmens and Parkes (8) subsequently investigated the androgenic and gynecogenic action of testosterone and methyl testosterone on capons, rats and rabbits by percutaneous, oral and parenteral administration. Testosterone was less active by mouth than by injection, in both the capon and the castrated male rat and with respect to uterus growth in castrated and immature rabbits. Methyl testosterone was, however, almost as active by mouth as by injection in causing progestational proliferation in rabbits; it had a greater activity by mouth in the other tests than testosterone (capon, castrated male rat). Methyl testosterone had a more potent androgenic action in the rat than testosterone but was less potent in capons. Methyl testosterone was always the more potent in progestational tests whichever route of administration was used. The two substances were about equally active in producing uterine growth in spayed rats and immature rabbits. On being tested for progestational activity by McPhail's method (9) methyl testosterone was found by Klein and Parkes (10) to be more potent than testosterone. These papers confirm the fact that methyl testosterone is the most potent of this class of compounds on administration by mouth.

Biskind (11) has also recently studied the question of the difference in potency between testosterone propionate and methyl testosterone on administration by mouth. He reached the conclusion that it is not due to a less pronounced decomposition of methyl testosterone by intestinal ferments but to a difference in the route of absorption; this may be, in the case of methyl testosterone, via the lymph vessels.

The activity of methyl testosterone when administered by mouth is well established from the evi-

dence of all of these publications. Clinical trials have also been made. Foss (12) succeeded in maintaining complete potency in a eunuch with 100 mg daily, even 50 mg a day proved to be effective. In cases of delayed development with genital hypoplasia, he succeeded in producing all signs of puberty, not only with regard to sexual organs but also in general physical development, with daily doses of 50 mg for a period of 57 days. In the opinion of the author, methyl testosterone orally is capable of replacing all other methods of treatment with male hormones. Favorable results in the treatment of prostatic hypertrophy are reported by Merk (13) who obtained a satisfactory hormone action with 15 to 30 mg a day.

More recently, Byron and Katzen (14), Kearns (15), Tager and Shelton (16) have also reported satisfactory results with methyl testosterone in eunuchism and genital hypoplasia. The external genitals increased in size, secondary sexual characteristics became more pronounced, and libido increased. Byron and Katzen observed in three eunuchs and one 10-year old boy with genital hypofunction a gain in weight, increase in basal metabolism and a pronounced stimulant action on thoracic tissue. Comparative studies with testosterone propionate indicated that a  $2\frac{1}{2}$  to  $3\frac{1}{2}$  times larger dose of methyl testosterone is required to produce the same effect as the injected male hormone.

Simonson, Kearns and Enzer (17) studied the influence of 4 weeks of methyl testosterone treatment on working capacity and endurance in two eunuchs and two castrates. The results show the definite increase of muscular performance and a slight increase of absolute muscular strength. McCullagh and Rossmuller (18) compared the clinical effects of methyl testosterone administered orally with those of testosterone propionate administered by injection. The 19 patients treated included cases of severe prepubertal hypogonadism, primary pituitary disease with secondary hypogonadism and functional impotence. The doses used varied from 25 to 300 mg daily. Methyl testosterone was shown to have pronounced androgenic activity.

Dorfman and Hamilton (19) also demonstrated the androgenic activity of methyl testosterone and other substances by estimating the excretion of ketonic and nonketonic androgens in the urine after oral administration. All of the substances investigated were absorbed from the gastrointestinal tract, methyl testosterone, although exerting a definite androgenic influence, produces only a slight increase in the concentration of androgens in the urine.

A clinical contribution to present knowledge of the favorable action of androgenic hormones in various disorders of the female genital tract has been made by Abarbanel and his coworkers (20). Follow-

ing the favorable results obtained with testosterone propionate by injection, methyl testosterone tablets have more recently also been used (21). Salmon et al (21) believe that this offers an effective form of androgenic treatment which will, after more experience has been gained, replace the others.

Spence (22) records results which allow some comparison of the various forms of treatment. Two cases of eunuchism and 4 of hypogonadism were treated with intramuscular injections of testosterone propionate, implantation of tablets of testosterone, inunction of testosterone propionate as an ointment or tincture and the oral administration of methyl testosterone. The corresponding maintenance doses required to produce about the same effect, as judged by the frequency and potency of erections, were: a) testosterone propionate intramuscularly, 50 to 75 mg per week, given in two or three injections; b) Daily inunction of testosterone propionate as an ointment, 32 to 49 mg per week; c) Daily inunction of testosterone as an ointment, 17.5 mg per week; d) Oral administration of methyl testosterone, 350 mg per week in doses of 10 mg 5 times a day.

As is known from the literature and as our own experience has confirmed, testosterone propionate is a very active hormone with which we can successfully treat a number of genital dysfunctions in the female. Testosterone propionate, however, has two disadvantages. Firstly, there is the necessity of repeated injections and, secondly, the arthenomimetic phenomena (change in voice, hirsutism and growth of clitoris).

In order to avoid these undesired symptoms we decided to carry out trials with sublingual therapy, in particular in women who suffered from climacteric disorders (pruritus, hot flushes and insomnia).

We were encouraged in these trials by the very good reports which had been published on the sublingual administration of desoxycorticosterone acetate. Anderson (23) found that desoxycorticosterone acetate dissolved in propylene glycol and administered by drops under the tongue is as effective as when it is given in oil subcutaneously or intramuscularly. These results were confirmed by Turnoff and Rowntree (24) who successfully treated 2 cases of Addison's disease with a solution of desoxycorticosterone acetate in propylene glycol. The patients were given 1 mg (6 drops) under the tongue, 6 to 7 times daily, the preparation being retained for 15 minutes and then expectorated. This method did not seem to be very convenient, however, so that we decided to use especially hard pressed tablets.

We treated in all 19 women varying in age between 27 and 67 years. Fifteen of the patients were suffering from climacteric symptoms, two from severe dysmenorrhea and two from mastodynia.



The most frequently occurring symptoms in the cases with climacteric disorders were found to be pruritus and insomnia. In the majority of cases other medicaments had been tried before methyl testosterone. In one case we observed favorable results with follicular hormone by injection, with follicular hormone ointment and with testosterone propionate by injection. In 14 of 15 cases, however, treatment with methyl testosterone was the most prolonged in effect and also the most convenient.

The dosage is, of course of decisive importance; as in hormone therapy in general, only a carefully chosen individual dosage gives satisfactory results. The method of application of the medicament might be briefly mentioned here. Thanks to the most recent knowledge on the considerably increased potency of hormones when administered sublingually, we used this method of administration in our cases. The tablets should be placed under the tongue and allowed to dissolve slowly with as little salivation as possible. The rapid and favorable effect of these tablets is explained as follows: absorption from the oral mucous membrane makes it possible to avoid the usual route through the liver, where the majority of substances undergo chemical changes and lose a large percentage of their activity; in addition the short route from the oral mucous membrane to the main vessels and the heart also favors absorption. The taste of the tablets is pleasant so that this method of application is appreciated by the patient.

The dosage given varied from one tablet of 5 mg. a day up to 30 mg. a day in severe cases. In six patients with insomnia and hot flushes, the administration of one tablet of 5 mg. every day for 2 months was sufficient. After only a few days there was slight improvement and after several weeks the symptoms had completely disappeared. These were, in general, mild cases although the usual sedatives were without effect.

Five other patients were suffering from persistent pruritus, partly with Kraurosis vulvae and leukoplakia, as a result of which there was severe insomnia. In four of these cases the complaints became less severe after treatment with 25 to 30 mg. (5-6 tablets) a day, so that the patients were able to sleep. Treatment had to be continued over a number of weeks, however, as there were otherwise cases of relapse. In one case of deficiency symptoms after roentgen-ray treatment of a uterine carcinoma, treatment with testosterone propionate in sublingual tablets was without success, but the pruritus and hot flushes were successfully treated with injections of 5 to 10 mg. of testosterone propionate 2 to 3 times a week. In the remaining 4 cases, pruritus, hot flushes and insomnia were successfully treated on an average with 2 or 3 sublingual tablets a day.

In two cases of dysmenorrhea, one of which concerned a 'neurovegetative stigmatic' with extensive genital hypoplasia, all forms of treatment including that with sublingual tablets failed. In the second case, however, the pains were somewhat alleviated by taking 30 mg. of methyl testosterone daily for 3 days before the expected menstruation and 2 days after it had started. In the 2 cases of mastodynia, the pains disappeared within a month with a dose of 15 to 30 mg. a day.

The preparation was well tolerated by all patients; no single case of nausea, or vomiting was experienced. With regard to the arrhenomimetic symptoms, such as growth of the clitoris, change in the voice and hirsutism, there occurred in one of the women a slight fluffy growth on the chin after having received 900 mg. of methyl testosterone sublingually within a month. This disappeared, however, a few days after discontinuing the treatment. In a number of patients who received large doses, smears were always taken, as experience has shown that the occurrence of the so-called atrophy cells (small epithelial cells with a large, dark-colored nucleus) is a symptom of follicular deficiency, which is the first alarm signal for overdosage and its subsequent symptoms.

In only one of the above mentioned cases were such atrophy cells present; in this case treatment was discontinued without further trouble for the patient.

The number of cases treated is much too small for far-reaching conclusions to be made. It is, however, seen that methyl testosterone as sublingual tablets constitutes an effective and convenient form of treatment of climacteric deficiency symptoms. We are justified even today in stating that tablets for sublingual dosage are well tolerated, comparatively harmless and have a prolonged action. By taking vaginal smears regularly twice a month characteristic alterations are recognized at an early stage and the disagreeable and undesirable effects of methyl testosterone can be avoided.

#### SUMMARY

A short review of the literature on experimental and clinical observations with methyl testosterone in males and females is given. A report is made on 19 cases (15 of climacteric disorders, 2 of dysmenorrhea and 2 of mastodynia) treated with methyl testosterone in sublingual tablets.

In moderately severe cases of climacteric disorders 2 to 3 tablets of 5 mg. each a day were sufficient; in more severe cases 25 to 30 mg. (5-6 tablets). In one case in which 900 mg. of methyl testosterone was given in one month, a slight growth of hair was produced in the chin; the hair disappeared within a few days after discontinuing treatment. Special atten-

tion is drawn to control of the dosage by means of vaginal smears in order to avoid any possible arthromimetic symptoms

Although the number of cases is small, the particularly favorable and convenient method of administration of methyl testosterone as sublingual tablets is illustrated, although this communication is meant to serve only as a stimulation to further investigation of this compound and its method of application

We wish to express our appreciation to the Society of Chemical Industry in Basle (Ciba) for supplying us with methyl testosterone sublingual tablets

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# Subjective Symptoms and Therapeutic Response in the Control of Estrogen-Progesterone Therapy in Menstrual and Reproductive Disorders

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IT HAS LONG BEEN OBVIOUS that the two ovarian hormones estrogen and progesterone have a definite relationship to each other and to menstrual and reproductive function. An antagonistic relationship between estrogen and progesterone was first suggested by Smith and Smith in 1931 (1). Prior to the presentation of a gravimetric method for the estimation of urinary pregnandiol by Venning (2) in 1937, endometrial biopsy was the only means available for the estimation of progesterone activity. Wilson, Randall and Osterberg (3) have presented evidence indicating that endometrial changes do not provide an accurate index to the variations of urinary pregnandiol levels. This observation would seem to indicate that endometrial changes are of qualitative rather than quantitative significance. Lack of quantitative means for the determination of progesterone activity has undoubtedly been responsible for the paucity of considerations of estrogen and progesterone relationship in the literature. Theories for estrogen and progesterone therapy have been based primarily on conclusions derived from the results of animal or human experimentation. In such experimentation the subject has invariably been either a normally functioning endocrine mechanism or a castrate. The favorable results obtained by the application of these theories in the treatment of menopausal disorders have not been duplicated when theories derived from experimental evidence in normal animals have been applied in the treatment of disorders resulting from abnormal endocrine function encountered prior to the menopause. In spite of the fact that some encouraging results have been reported in the treatment of threatened abortion, habitual abortion, dysmenorrhea, menorrhagia and metrorrhagia with progesterone, and in nausea and vomiting of pregnancy and certain other premenopausal disorders with estrogens,

the results have not been comparable to those obtained in menopausal disorders. Consideration of the results in the present series of cases suggests the possibility that the attempt to apply such theories in ovarian imbalances prior to the menopause may be an important factor in the failure to obtain more consistent results with estrin and progesterone therapy.

In the present series of 578 cases, the observation (4) that menstrual and reproductive disorders due to estrogen and progesterone imbalances were always accompanied by many of the same subjective symptoms encountered in the menopausal deficiencies was utilized. The presence of such symptoms was accepted as evidence of estrogen-progesterone imbalance, while response to therapy in the form of relief or exaggeration of these symptoms served as evidence of the type of deficiency which existed.

Because of the importance of meticulous consideration of detail, the syndrome previously described (5, 6) is again presented.

*Syndrome suggestive of estrogen-progesterone (5) imbalance prior to the menopause.* a) exhaustion; b) nervousness and irritability; c) depression; d) emotional instability; e) breast tenderness; f) cramping or bearing down; g) neckache; h) legache; i) headache with or without nausea; j) backache; k) insomnia; l) dizziness; m) hot flushes; n) vaginal irritation; o) frigidity; p) psychotic disturbances such as apprehension of social contacts, disturbing dreams, and suicidal or homicidal tendencies.

*Associated conditions.* a) hypertension; b) atrophic rhinitis; c) irritable colon; d) arthralgias; e) skin eruptions; f) migraine (menstrual or menopausal); g) pelvic pain in the absence of pathologic findings.

In the present series of cases all patients in whom any combination of symptoms of the above syndrome was encountered in association with disturbance of menstrual function were placed on estrogenic therapy. Relief of subjective symptoms with improvement or

relief of the accompanying disturbances occurred in a large percentage of these patients. The method of diagnosis and determination of dosage has been previously described (6), and only the essentials are again presented. These essentials are based on the observation that the exact amount of estrogenic substance<sup>1</sup> when administered parenterally will relieve subjective symptoms within 45 minutes for a period of 6 or 8 hours or longer. These amounts rarely exceed 300 i.u., and dosage in each individual is begun with 100 i.u. and continued in daily injections.

In a small but rather definite group, however, it was not only impossible to obtain relief but also both subjective symptoms and abnormal menstrual conditions appeared to be definitely exaggerated or intensified. Cessation of estrogenic therapy was consistently followed by prompt decrease in exaggeration of the

estrogen or progesterone deficiency, and led to the hypothesis that menstrual and reproductive function might be dependent on balance between estrogen and progesterone.

*The essentials of therapeutic response* (6). It has been observed that three types of reaction occur following parenteral administration of estrogenic sub-

TABLE 2

|              | No Cases | Successes |            | Failures | Incomplete |
|--------------|----------|-----------|------------|----------|------------|
|              |          | Estrogens | Progestone |          |            |
| Dysmenorrhea | 71       | 54        | 12         | 4        | 1          |
| Menorrhagia  | 113      | 61        | 36         | 14       | 2          |
| Metrorrhagia | 10       | 5         | 2          | 3        | 0          |
|              | 194      | 120       | 50         | 21       | 3          |

TABLE 1

|   | No Cases | Successes |            | Failures <sup>1</sup> | Incomplete |
|---|----------|-----------|------------|-----------------------|------------|
|   |          | Estrogens | Progestone |                       |            |
| <b>Group A</b>                            |          |           |            |                       |            |
| Menopausal disorders                      | 107      | 103       | 0          | 3                     | 1          |
| Amenorrhea, oligomenorrhea, hypomenorrhea | 96       | 77        | 3          | 10                    | 6          |
| Totals for Group A                        | 203      | 180       | 3          | 13                    | 7          |
| <b>Group B</b>                            |          |           |            |                       |            |
| Premenopausal <sup>2</sup>                | 38       | 27        | 2          | 6                     | 3          |
| Dysmenorrhea                              | 71       | 54        | 12         | 4                     | 1          |
| Menorrhagia                               | 113      | 61        | 36         | 14                    | 2          |
| Metrorrhagia                              | 10       | 5         | 2          | 3                     | 0          |
| Sterility                                 | 57       | 16        | 7          | 24                    | 10         |
| Habitual abortion                         | 16       | 9         | 7          | 0                     | 0          |
| Threatened abortion                       | 24       | 7         | 5          | 11                    | 1          |
| Nausea or nausea and vomiting             | 46       | 28        | 17         | 0                     | 1          |
| Totals for Group B                        | 375      | 207       | 88         | 62                    | 18         |
| Total cases                               | 578      | 387       | 91         | 75                    | 25         |

<sup>1</sup> Partially successful results were classified as failures.

<sup>2</sup> Women of menopausal age who presented only subjective symptoms and no complaints permitting classification under other categories.

condition. In most of the cases in this smaller group the administration of progesterone produced clinical results comparable to those obtained by estrogenic therapy in the larger group. The consistency with which these results were obtained when applied in menstrual disorders, and in sterility, habitual abortion, and nausea and vomiting of pregnancy, indicated that the syndrome originally described (4) as suggestive of estrogenic deficiency, might when encountered prior to the menopause, be due to either

stances. These reactions occur within one hour after administration and though transitory are of considerable significance. These reactions are a), total absence of effect which usually indicates that estrogenic deficiency exists and that the initial dose has been inadequate and should be increased, b) an improvement or relief of symptoms, or a feeling of wellbeing for a period of 6 to 8 hours which is evidence that an actual estrogenic deficiency exists and therapy should be continued, c), an exaggeration of the symptoms, extreme exhaustion, pelvic pain, or bearing down sensation, if transitory and followed by relief of the original symptoms, indicates that estrogenic deficiency exists but that dosage was excessive and should be decreased, if prolonged and not followed by relief of original symptoms, that estrogenic deficiency does not exist and that progesterone therapy is indicated.

In the present series, for the purpose of classification, only the most obvious disturbance or complaint was utilized when several conditions existed simultaneously.

Table 1 demonstrates the presence of two distinct therapeutic types which have been separated into groups A and B. It will be noted that in group A, consisting entirely of various forms of amenorrheic disorders, successful results were obtained in almost 90 per cent of the cases with the estrogens. In group B, composed of various forms of menstrual and reproductive disturbances successful results were obtained in over 50 per cent of the cases by means of the estrogens, while less than 25 per cent of the total number responded in a like manner to progesterone therapy. These results would seem to be logical in view of the rather well established fact that absence of ovulation in amenorrheic conditions results in absence of progesterone activity, while in the pres-

<sup>1</sup> The estrogen (Amniotin in oil) was supplied by E. R. Squibb and Sons, New York City.

ence of ovulation or placentation in other menstrual and reproductive disorders progesterone activity is always a factor which must be considered.

Further analysis of group B reveals that of the 38 cases classified as premenopausal the predominant deficiency was estrogenic, only 2 patients responding to progesterone.

The results in dysmenorrhea, menorrhagia, and metrorrhagia, as demonstrated in table 2, indicate estrogenic deficiency as a more frequent etiologic factor than progesterone deficiency. In each of these conditions, contrary to expectations based on our concept of progesterone activity, a far greater number responded to estrogenic therapy than to progesterone, 120 being relieved by the estrogens as compared to 50 responding to progesterone.

TABLE 3

|                     | No. Cases | Successes |              | Failures | Incomplete |
|---------------------|-----------|-----------|--------------|----------|------------|
|                     |           | Estrogens | Progesterone |          |            |
| Habitual abortion   | 16        | 9         | 7            | 0        | 0          |
| Threatened abortion | 24        | 7         | 5            | 11       | 1          |
| Totals              | 40        | 16        | 12           | 11       | 1          |

The results in threatened and habitual abortion in table 3, although the number of cases is too small to permit conclusive deductions, are of interest and possible importance. In 16 cases of habitual abortion (previous losses of 2 or more pregnancies) all were carried to successful termination with a living child in each instance. In 9 cases this was accomplished with estrogenic therapy, and in 7 with progesterone. In every instance therapy was instituted either prior to conception or early in pregnancy prior to any threat to abort. In contrast in the 24 cases of threatened abortion where therapy was not instituted until after manifestations such as bleeding and cramping had occurred, it was possible to preserve the pregnancy in only 12 or 50 per cent of the cases. Here

again the preponderance of estrogenic deficiency as an etiologic factor is indicated, with 7 cases responding to the estrogens and 5 cases to progesterone.

The series of 57 cases of sterility listed in table 1 included only those in which tubal occlusion and male sterility had been eliminated. The fact that pregnancy occurred in 23 cases following therapy would indicate estrogen and progesterone imbalance as an etiologic factor of considerable importance.

CONCLUSIONS

In the present series of cases, subjective symptoms and therapeutic response have been used, both as a diagnostic measure to determine the type of deficiency and as criteria for dosage.

Relief of subjective symptoms was accompanied by correction of the conditions presented by the patient in an impressive percentage of the cases treated.

The results would seem to suggest that a), menstrual and reproductive function may be dependent on balance between estrogen and progesterone; b) that estrogen and progesterone deficiencies may be relative rather than quantitative; c) that subjective symptoms and therapeutic response may be utilized as therapeutic guides until more accurate methods become available, and d) that failure to obtain consistent results in many of these conditions may have been due to excessive therapy.

The hormone preparations were supplied by Ayerst, McKenna & Harrison, Ltd., Rouses Point, N.Y., E. R. Squibb & Sons, New York City and The Schering Corporation, Bloomfield, N. J.

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# Weekly Urinary Pregnanediol Determinations throughout the Last Seven Months of Pregnancy in Two Cases of Primary Sterility

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TWO CASES OF PRIMARY STERILITY 7 and 4 years in duration respectively, are presented. By means of the Rubin and Huhner tests, tubal occlusion and male sterility had been excluded. Daily vaginal smears over a period of several months in 1938 suggested estrin deficiency in one patient and progesterone deficiency in the other. By utilizing subjective symptoms, therapeutic response, and the vaginal smear (1-4), adequate dosage was determined in each instance and the patients placed on the therapy indicated. Pregnancy occurred almost simultaneously in both patients within three months, and in each instance was accompanied by nausea and vomiting at 6 to 8 weeks, and by threat to abort manifested by bleeding and cramping. These disturbances were relieved by continuation and regulation of estrogenic therapy in one patient, and progesterone in the other. In the patient presenting estrogenic deficiency, therapy was continued until the fourth month, while in the patient having a progesterone deficiency, therapy was continued until the seventh month. Weekly urinary pregnanediol determinations were obtained in each case during the last 7 months of pregnancy.

## CASE HISTORIES

**Case 1** The patient, 28 years of age, was first seen on December 14th, 1937, with a primary sterility of 7 years' duration. The menses began at 11 years of age, were of the regular 28 day type, lasting 3 to 4 days, and were moderate to scant in amount, with no pain. Prodromal symptoms consisted of breast tenderness, nervousness, irritability, depression, and exhaustion, and were variably present for 1 or 2 days prior to the menses. Tubal patency was confirmed on Jan. 4th, 1938, by the Rubin method, the gas passing easily at 70 to 80 mm. of Hg. The Huhner test revealed normal spermatozoa in the husband. Vaginal smears suggested estrogenic deficiency and therapy was instituted

in February 1938. Breast tenderness, cramping, and depression were definitely relieved by estrogens.<sup>1</sup> The last menstrual period occurred April 21st, 1938, and the pregnancy test was negative on May 25th, 1938, but positive when repeated on June 3rd, 1938. Nausea and vomiting began on May 24th, 1938, and at the same time threat to abort with cramping and bleeding occurred, both conditions being relieved by increasing the daily dose of estrogen. All medication was discontinued on Aug. 10th, 1938, and pregnancy progressed uneventfully to term on Jan. 28th, 1939, with spontaneous delivery of a normal female child weighing 7 lb. 3 oz.

**Case 2** The patient, 26 years of age, with a primary sterility of 4 years' duration, was first seen on Nov. 30th, 1936. There was a history of appendectomy and oophorectomy within the first year of marriage. Previous tubal inflation and Huhner tests by competent obstetricians, repeated twice within three years, were accepted as evidence establishing tubal patency in the patient, and the presence of normal spermatozoa in the husband. The menses which had started at 12 years of age were irregular at 26 to 31 day intervals, lasting 8 days, and excessive with no pain or history of prodromal symptoms. Examination revealed a small infantile uterus to the right of the midline, the right ovary could not be palpated, and the left ovary was slightly enlarged. Endocrine therapy was administered from Jan. 21st, 1937, to Aug. 2nd, 1937, with the result that when estrogenic therapy produced extreme vaginal irritation, and subsequent progesterone therapy caused cramping, medication was discontinued as unsatisfactory. Pregnancy occurred 4 months after cessation of therapy but was followed by abortion in spite of the administration of progesterone. The last menstrual period had occurred on Dec. 23rd, 1937, cramping and bleeding beginning on Feb. 9th, 1938. Pregnancy test was positive on Feb. 10th, 1938, and abortion occurred on Feb. 24th.

On the assumption that the previous endocrine therapy must have been responsible for the pregnancy, daily vagi-

<sup>1</sup> The estrogens (Amniotin and Emmenin) were supplied by E. R. Squibb and Sons, New York City and by Ayerst, McKenna and Harrison, Ltd., Rouses Point, N. Y., respectively.

nal smears were taken from April 23rd to June 2nd, 1938. These smears indicated a progesterone deficiency. The patient reported extreme exhaustion on May 31st, 1938, and progesterone<sup>2</sup> relieved the exhaustion within one hour. Progesterone, 1/10 rb.u. was administered on June 2nd, and 4th, July 5th, and 7th; 1/5th unit on July 11th, 14th,

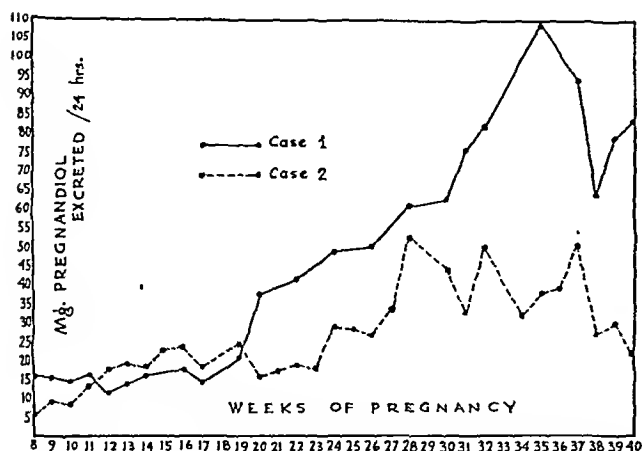


Fig. 1. WEEKLY PREGNANDIOL EXCRETION VALUES in cases 1 and 2.

16th, 19th, 25th, Aug. 1st, and 4th, 1938. The last menstrual period occurred on June 15th, 1938. Pregnancy test became positive on July 28th, 1938, nausea and vomiting, headache, exhaustion, and backache and cramping, accompanied by slight bleeding occurred on Aug. 8th, and were controlled from Aug. 8th to Jan. 12th, 1939, with 21 injections of progesterone ranging from 1/4th to 1/10th rb.u. doses. No additional therapy was necessary thereafter and the pregnancy terminated normally with the delivery of a 6 lb. female child on March 24th, 1939.

#### DISCUSSION

Weekly determinations of urinary pregnandiol were obtained throughout pregnancy beginning at the eighth week in both instances. The method described by Venning (5) was utilized and all determinations were carried out on the urinary excretion for 24-hour periods. Therapy was continued in case 2 until the 30th week of the pregnancy and until week 16 in case 1. In both patients complete abeyance of symptoms was obtained and the usual discomforts encountered during pregnancy were notably lacking. In figure 1, the pregnandiol determinations of case 1 are represented by the solid line, those of case 2 by the broken line, the vertical plane representing the milligrams of pregnandiol, and the horizontal representing the weeks of pregnancy. It is of interest to note that the two curves are almost analogous to the highest and lowest levels presented as normal limits during pregnancy by Venning and Browne (6), and also correspond to the high and low values as indi-

cated by Wilson, Randall and Osterberg (7). Case 1 in which the evidence would indicate a relative deficiency of the estrogens and an excess of progesterone provided the maximum curve, while in case 2, in which the evidence suggested an excess of the estrogens with a deficiency of progesterone, the minimal pregnandiol values occurred. These values in case 1 ranged from 16.95 mg. at week 8 to a maximum of 109 mg. at week 31, decreasing thereafter only to 64.27, 79.75, and 83.69 mg. at weeks 38, 39, and 40 respectively. In case 2 the pregnandiol levels ranged from 5.97 mg. during week 8 to a high of 52.45 mg. at week 27, and with a decrease to 26.35, 30.02, and 22.85 mg. at weeks 38, 39, and 40 respectively.

The difference in the levels of pregnandiol excretion and the normal course of the prenatal period and labor in these two cases after correction of estrogen and progesterone imbalance would seem to indicate that while therapy seems to have been of clinical value in overcoming sterility, nausea and vomiting, and threatened abortion, there is no evidence which indicates that therapy in either case influenced the pregnandiol levels. Despite the fact that low pregnandiol levels were encountered in the patient where progesterone therapy was of clinical value, and abnormally high pregnandiol levels were obtained in the case where estrin therapy produced clinical results, there is no evidence that therapy in either instance produced a demonstrable change in the pregnandiol values. If correct, this observation would tend to corroborate the suggestion by Novak (8) that balance between estrogen and progesterone, rather than quantitative values is the important factor. The extremely small dosages used in comparison with the present tendency toward massive dosages are considered by the author as a significant factor in the results obtained.

The author desires to express his appreciation to Doctor G. E. Wakerlin, chief of Department of Physiology, University of Illinois School of Medicine, for his cooperation in obtaining the urinary pregnandiol determinations which served as the basis for this study.

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# Adrenal Tumor in Female Infant

With Hypertrichosis, Hypertension, Overdevelopment of External Genitalia, Obesity, but Absence of Breast Enlargement

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THE SEX AND AGE of the individual have an influence upon the character of the symptoms and functional disturbances produced by tumors of the adrenal gland whether these are benign or malignant, for instance, the term 'Cushing's syndrome' does not cover the various types which have recently become known. Case reports confirm the occurrence of certain common characteristics, but as in most diseases, an analysis of the symptomatology may show variations. Sexual precocity in the young boy, enlarged mammary glands in the adolescent male and masculinization of the preadolescent female, are examples of such clinical endocrine abnormalities.

The case reported here is that of an infant, with a syndrome which is especially characteristic in a young female child who has an adrenal cortical tumor. Lissner<sup>(1)</sup> has termed this "pseudo sexual precocity" to distinguish it from "true sexual precocity" caused by tumors of the ovary of the granulosa cell type.

## CASE REPORT

*Baby Girl X* was born July 8, 1939, weighing 7 3/4 pounds, height, 21 inches. She gained steadily and at 7 months the weight was 18 pounds, the height 28 5/8 inches. At 8 months changes in appearance began with an unusual growth of body hair, at 11 months acne appeared and continued on the face and chest. The teeth and weight were normal at one year of age.

*Findings at sixteen months.* On Oct. 29, 1940, the patient was admitted to the hospital. There was a tendency to obesity, she was able to stand but was not walking much. There was a generalized hirsuties, heaviest over the back, shoulders, axillae, and genitalia. The labiae were hypertrophied, and of adult appearance.

The blood pressure varied from 140 to 180 mm Hg sys

## [[Pseudo-Sexual Precocity]]

tolic. The red blood cell count was 6,830,000 and the hemoglobin 76 per cent. The blood chemistry findings were normal, including sugar and glucose tolerance. The non-protein nitrogen was 34.5 mg per cent, the sodium chloride 460 mg per cent.

*Roentgenogram.* The spine, pelvis and hips were normal in form but the bones were massive and the ossification centers were advanced to 2 years or more. The skull was large, the sella turcica was small. By aid of a retrograde pyelogram, a mass was seen surmounting the upper pole of the left kidney. A stereogram indicated a mass adjacent to the posterior rather than to the anterior portion of the upper pole.

*Cystoscopic examination.* Seven cc of urine was collected at once from the left ureteral catheter which was indicative of a pathological state on that side.

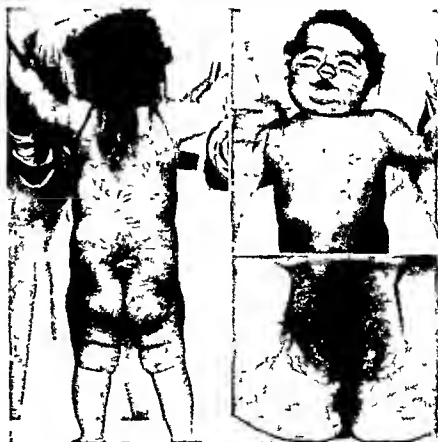


Fig. 1. APPEARANCE OF INFANT ON ADMISSION TO HOSPITAL AT AGE OF 16 MONTHS

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**Air injection.** A tumor mass was outlined by a small amount of air introduced into the perirenal space.

Operation was delayed nearly one month because of an

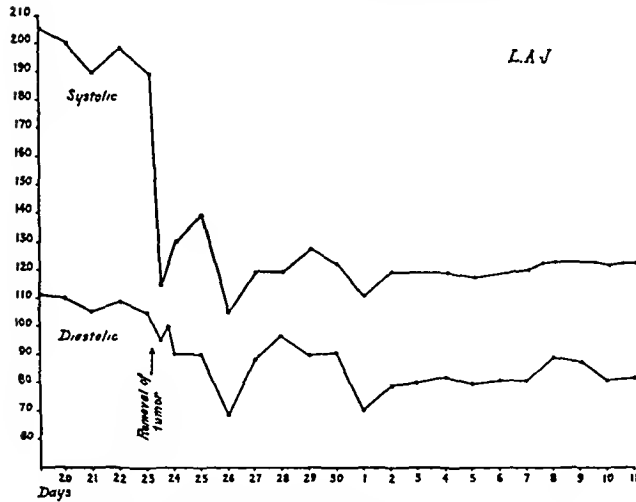


Fig. 2. CHART OF BLOOD PRESSURES RECORDED BEFORE AND AFTER OPERATION FOR ADRENAL TUMOR.

intercurrent upper respiratory infection. During the weeks that elapsed after the foregoing diagnostic measures were made, the tumor became palpable.

**Preoperative findings.** The blood pressure was 200 mm. Hg systolic, 110 diastolic. A few days were allowed for preparation (2) of the patient consisting of a potassium-free diet and sodium chloride and citrate given liberally.

**Operation, Nov. 23, 1940.** The patient was placed on the table with her right side downward. Two large adhesive strips were used to fasten her securely to the table. The table was then broken so that the greatest amount of space could be obtained in the loin. A curved lumbar inci-

sion was made exposing the perirenal space. The kidney was picked up and the fatty envelop opened. When the kidney was pushed down, the tumor presented itself as a rounded mass in the area of the dome of the diaphragm. This was quickly dissected free and pulled downward. The vein going into this tumor presented toward the operator. This vein was grasped with a clamp in order to prevent the hormone going into the blood stream. The pedicle to this tumor was then clamped and tied, and the tumor freed and cut away. During the operation the blood pressure rose to 180 and then to 200 mm.Hg. It fell as soon as this vein was clamped, but it did not go lower than 80 mm.Hg systolic. The patient was taken from the operating room in good condition. Immediately afterward the white cell count was found to be 44,850 with 84 per cent polymorphonuclear leucocytes. The count gradually fell to a normal level.

The blood chemistry, including non-protein nitrogen, creatinine, and sugar were within normal limits on Nov. 22, 25, and Dec. 4. The sodium chloride was 301.7 mg. on Nov. 23; 326.7 mg. on Nov. 25; and 329.6 mg. on Dec. 6.

**Treatment.** Adrenal cortical hormone and fluids by clysis were used during and following the operation. Sedation was with paregoric. The infant was dismissed as well on Dec. 11, 1940.

**Characteristics of the tumor.** The tumor weighed 96 grams; it was spherical in shape and 6 cm. in diameter. There was a thin capsule; a portion of adrenal cortical tissue 10×2×2 mm. could be identified on the surface.

Histologically the growth consisted of small groups of round, oval, or polyhedral cells with abundant cytoplasm; they were separated by delicate septa of con-

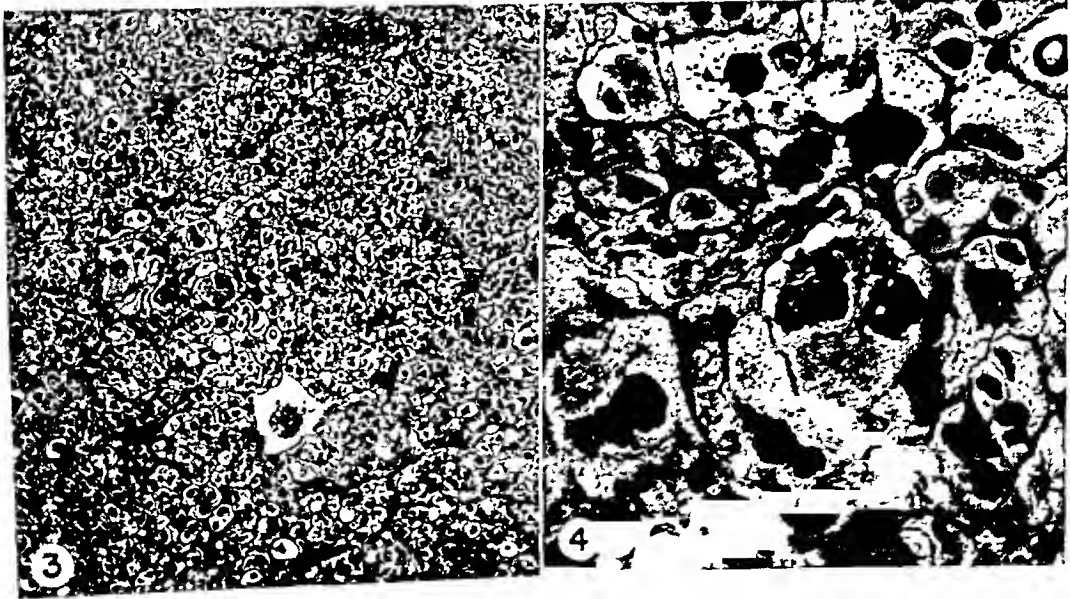


Fig. 3. PHOTOGRAPH OF TUMOR SECTION. This shows the solid cellular structure, without definite septa or any tendency to alveolar formation. Note the intimate relation of the tumor cells to the endothelium of the capillaries.  $\times 100$ .

Fig. 4. PHOTOGRAPH OF TUMOR SECTION. This shows the marked variation in size and shape of the cells, variable staining reaction of the nuclei, hyperchromatism and several multinucleated giant cells of neoplastic type. Note the pale staining areas in the cytoplasm of many cells. These areas proved to be lipid material.  $\times 460$ .

nective tissue (fig. 3 and 4). Numerous giant cells with single or multiple nuclei were present. There was considerable variation in the structure of the nuclei, many being large, irregularly lobulated and hyperchromatic; mitotic figures were frequently seen. Many cells showed vacuolization of the cytoplasm and gave positive reactions with fat stains. Brown granules were seen in many of the cells when the tissue was treated with chrome salts; silver impregnation permitted a diagnosis of chromaffinoma or pheochromocytoma.

*Degree of recovery following removal of the tumor.* Within 3 months most of the hirsutism had disappeared; the acne was less noticeable. The child's activity level became normal and there was a loss of some of the abundant fat which had been noticeable about the cheeks and the middle of the body. Six months after the operation the labiae and the pubic hair were less prominent. The axillary and dorsal hair had entirely disappeared.

#### DISCUSSION

It is difficult to correlate the structure of this tumor with the disturbances in physiology and changes in appearance of the child. It is known that there are one or more hormones produced in the adrenal cortex which play a part in the normal sexual development. In most of the examples of adrenal tumor associated with disturbances in development of sexual characteristics there has been a tumor of the cortex and usually a precocious development of male characteristics. However, there are reports of cases in which a tumor of the adrenal cortex has been associated with feminization, gynecomastia, atrophy of penis and testes, loss of libido, and usually with obesity. Hence it appears that adrenal cortical tumors may cause a disturbance of sexual development in either direction. The tumor presented here is a medullary tumor and would not be expected to cause any sexual changes. Ordinarily a medullary tumor is associated with paroxysmal hypertension, which was present in this case. One can only suggest that this tumor interfered with the function of the cortical tissue through mechanical effects. The portions of adrenal cortex stretched over the surface of the tumor were distinctly separated from it by a capsule. This cortical tissue was not atrophic and presumably it was producing an increased amount or a perverted type of secretion which may be held responsible for the changes noted clinically.

The fact is recognized that the two parts of the adrenal gland produce tumors that are entirely different pathologically. The two better known varieties of tumor developing in the medulla are the neuroblastoma and the ganglioneuroma; but the third variety, the paraganglioma, affects chromaffin cells not



Fig. 5. APPEARANCE OF CHILD AT 2 YEARS OF AGE, 9 MONTHS AFTER OPERATION FOR REMOVAL OF ADRENAL TUMOR

only in the medulla but in other regions of the body. The paraganglioma seems to be found in advanced life usually and may occur in either sex. A chromaffin tumor of the extramedullary type is said to produce the characteristic epinephrine.

In this case, the medullary tumor grossly seemed to be distinct from any connection with the cortex, because of a thick capsule. Eisenburg and Wallerstein, (3) in discussing paraganglioma, state that in most of these tumors, especially the large ones, the entire gland is involved in a tumor mass which obliterates the medulla but retains a thin rim of cortex.

The relationship between the pituitary gland and the adrenal cortex has recently been reviewed by Swann (4). He has found that control by the pituitary varies from maximal to minimal and is complete with respect to fat, protein, and sugar metabolism; control by the pituitary is possible but not proven in experimental hypertension.

An involvement of the adrenal by tumor makes it necessary to have a reservation as to what the growth will finally prove to be. Whether this tumor is benign will require prolonged observation of the patient, since carcinoma or a mixed tumor of the adrenal, with metastasis, is the most common final diagnosis.

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# Pituitary Antagonists in the Treatment of Bronchial Asthma

## [[Estrogenic Therapy in Asthma]]

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CLINICAL OBSERVATIONS of the marked influence of the emotions upon allergic diseases, such as asthma and urticaria, and experimental evidence pointing directly to modification of the localization and severity of atopic reaction through the autonomic nervous system, have led to general acceptance of the importance of the autonomic nervous system as a factor in the mechanism of such reaction (1). Modern therapy of diseases in this group makes use of agents affecting the nervous system. General sedatives, calcium and the parathyroid hormone, atropin, aminophyllin and epinephrin are of this nature. Of these epinephrin is the most effective, but the short duration of its action, the failure of its chronic administration to bring about sustained improvement, and especially the development of so-called adrenalin resistance,<sup>1</sup> indicate that it has no power to modify fundamentally any nervous system disturbance which might be responsible for the appearance of the allergic reaction.

Since the autonomic nervous system and the endocrine glands are closely associated both anatomically and functionally it would appear that hormonal balance could have some bearing upon susceptibility to atopic response. Evidence for the validity of this concept is furnished by the common observation that allergic states are prone to change markedly at puberty, during the various phases of the menstrual cycle, pregnancy, and the climacteric. That such changes are not consistent, being in one individual in the direction of improvement and in another for the worse, may argue against direct hormonal effect, but does not argue against some mediate hormonal effect, such, for example, as disturbance of autonomic balance.

The following report is of a case of Dr. R. B. Poling of Youngstown, Ohio. We have had the opportunity to follow the progress of the patient over a period of four and one-half years of illness. During the last twenty-four months of this period she had allergic vasomotor rhinitis and bronchial asthma. This pa-

tient has furnished an opportunity for observations bearing on the nature of the endocrine-autonomic-allergic mechanism. Her repeated response to sex hormone therapy is the most important of these observations.

### CASE REPORT

A white female, married, mother of 5 children, had never had allergic manifestations. A paternal aunt, a sister, and the son of a brother had had severe bronchial asthma most of their lives. A niece had had vasomotor rhinitis appearing coincidentally with neuro-vascular menopausal disturbance, both apparently having been benefited by estrogen administration. Another niece and another nephew are now suffering from asthma.

The patient had a large nodular thyroid which had remained unchanged for at least forty years. She had gone through an uneventful climacteric, the menses ceasing in the late forties, with no evidence of thyroid disturbance.

In January 1937 at the age of 75 years she had the first serious illness of her life. This was a generalized fibromyositis which gave rise to a low grade fever, constant pain, sleeplessness and a weight loss of 50 pounds. With the use of sulfanilamide and the removal of two infected teeth this condition subsided at the end of six months. In October 1937 manifest hyperthyroidism developed. In December, 1937 a sub-total thyroidectomy was performed.<sup>1</sup> Convalescence was satisfactory and relief of the symptoms of hyperthyroidism seemed complete.

In May 1939 there developed what the patient considered to be a peculiar head cold with a profuse nasal discharge. In the next month she became somewhat short of breath on exertion, and in early July began to have paroxysms of coughing. The diagnosis of bronchial asthma was made, and she was treated by the usual routine including epinephrin. Beginning at this time and re-appearing each time her asthma became worse, were sudden sweats which at times were drenching. These came without apparent immediate cause, and were dismissed as being an expression of her weakness, probably contributed to by increased respiratory effort and confinement to bed. At first she responded readily to epinephrin, but by the end of July she was in status asthmaticus and was taken to the hospital and kept in an oxygen tent for two weeks. Skin

<sup>1</sup> The subtotal thyroidectomy was performed by Dr. Carl Lenhart.

tests, direct and by passive transfer, were done and sensitivity to house dust was discovered. The blood eosinophil count was 11%. Dust extract injections were begun and continued until a month before death. On Aug 14, 1939, while still using as many as 7 injections of one-fourth cc. each of epinephrin per 24 hours, the patient returned

vasomotor rhinitis and sweats. In April 1940 she began to require more epinephrin and by the end of that month she was again in severe status asthmaticus.

On May 5, 1940 a vaginal smear was taken and found to be of atrophic type. On May 6, 1940, stilbestrol<sup>2</sup> 1.0 mg daily by mouth was begun. Three days later, on May 9 the

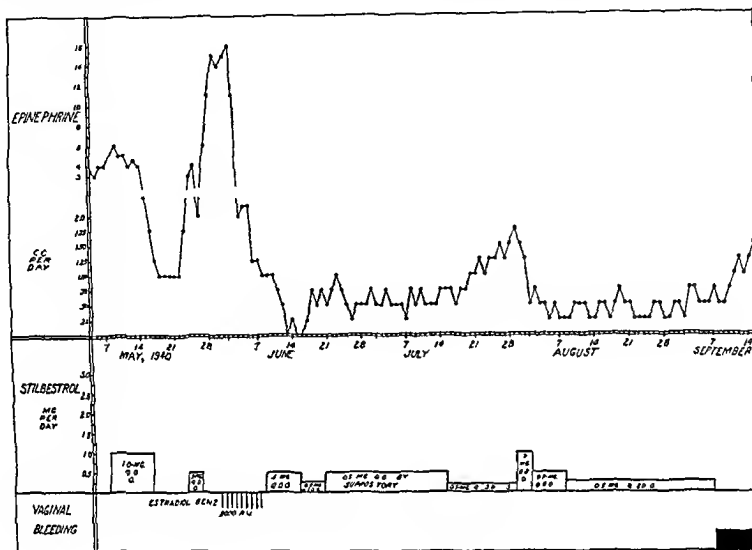


Fig 1 EPINEPHRIN REQUIREMENT during course of treatment, May to September, 1940

home to an 'allergen free' room with linoleum floor, no bangings, pollen air-filter in the window, and allergen-proof casings. Epinephrin spray, epinephrin in oil, elimination diets, aminophyllin and histaminase<sup>2</sup> were tried without apparent advantage over the previous therapeutic regime. From Sept 1, 1939 she became progressively worse and was returned to the hospital Sept 24, 1939, in severe status asthmaticus, using as much as 6 cc of epinephrin per 24 hours with little relief. The use of an oxygen tent seemed to benefit her. During this hospital stay X-ray irradiation to the lungs was given. The patient returned home on Oct 15, 1939, using 3 to 4 one-fourth cc epinephrin injections per 24 hours. During the winter of 1939-1940 she was relatively comfortable, remaining in her room most of the time, attended by a nurse, she used epinephrin several times each day. There was no time when she went without epinephrin longer than 12 hours. In those periods when the asthma was worse she also had

asthma was unrelieved and she returned again to the hospital. On May 15 she was much improved and on May 16 all medication except epinephrin was discontinued. One week later she began to get worse and stilbestrol was resumed, 0.5 mg per day. Because of nausea and vomiting which was probably not due to the amount of the drug, it was discontinued after three days. With but slight interruption the asthma became rapidly more severe and by May 30, in spite of all the accepted means of treatment, oxygen and helium, epinephrin to 16 cc per day, intravenous glucose and aminophyllin, her condition was desperate. She could no longer sleep, eat, or talk. Her death was considered imminent. Two thousand R.U. per day of estradiol benzoate by intramuscular injection was begun on May 30. On June 3 she required but 12 injections of one-fourth cc each of epinephrin, and it was certain that she had improved. On June 8, stilbestrol 0.5 mg daily by mouth, was substituted for estradiol. On June 13, 15, and 16 she used no epinephrin. She left the hospital on June 21. Her progress since May 4, 1940, as measured by 24 hour requirement of epinephrin, and related to pituitary antagonistic therapy, is shown in the figures. She remained in her room during those periods of exacerbation of asthma which occurred when the estrogen was withdrawn because uterine bleeding had appeared, once in July, 1940

<sup>2</sup> The histaminase was supplied through the courtesy of the Winthrop Chemical Company, New York City.

<sup>3</sup> The stilbestrol used in this case was furnished by Sharp & Dohme, Baltimore, Md., through Dr. J. L. McCartney, and by Eli Lilly & Co., Indianapolis, Ind., Dr. D. C. Hines. The testosterone propionate was furnished by The Schering Corporation, Bloomfield, N. J., the kindness of Dr. William Stoner.

on low dosage of stilbestrol. At other times the patient was up and about the house until December, 1940. There were three occasions, each one shortly after resumption of estrogen therapy, when she was without need of epinephrin for 48 hours or longer. From Jan. 1 to 10, 1941, she used only 3 injections of one-fourth cc. each of epinephrin; in this period she went 5 successive days with no epinephrin. During the remainder of the time when the asthma was under control she needed one-fourth cc. injections of epinephrin from one to three times in 24

still greater improvement. In September, 1940 therefore, when stilbestrol had been stopped because of uterine bleeding, it was resumed at a higher dose level. The resultant improvement was little greater than on the lower dose. On Nov. 20, 1940, when bleeding again occurred, instead of stopping stilbestrol the dose was raised from 1 mg. per day to 2 mg. per day in the hope that a dosage larger than the threshold dose might cause a cessation of flow (2). The

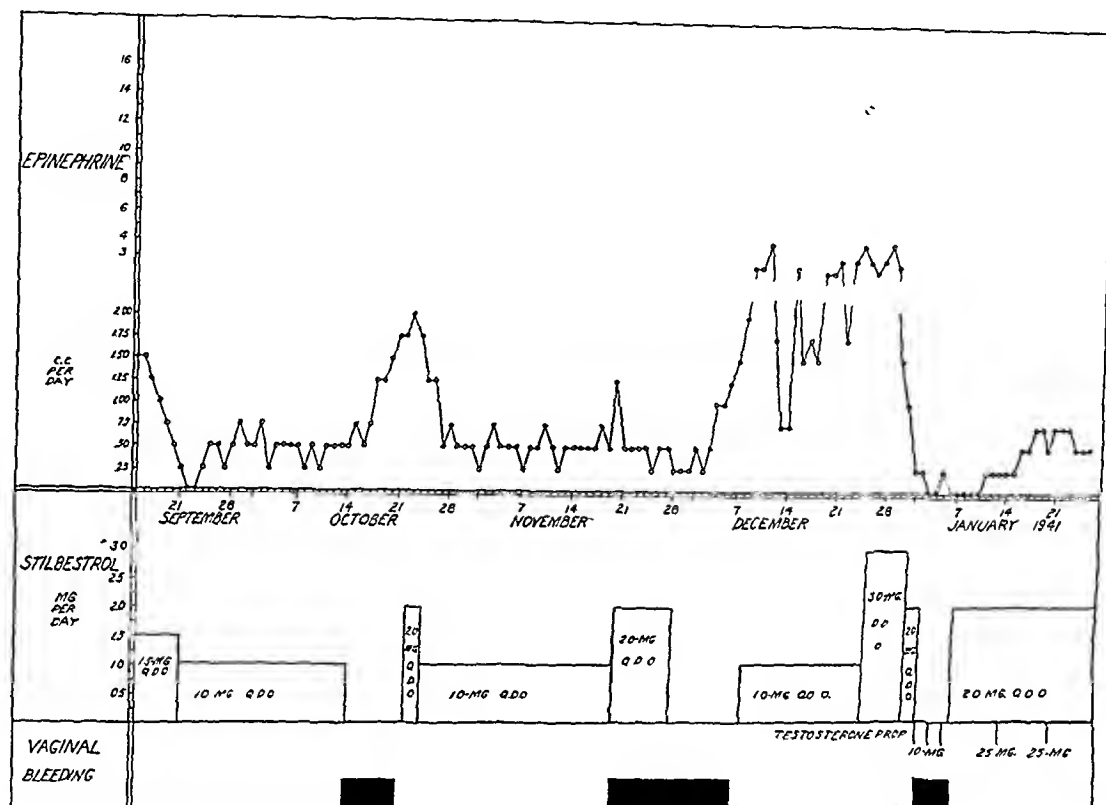


Fig. 2. EPINEPHRIN REQUIREMENT from September, 1940, to January, 1941.

hours, mostly at night. From February 1941 to the time of her death in June she had very few comfortable days.

#### DISCUSSION OF DATA

Figures 1 to 3 show the relations between the intensity of the asthma, as represented by the amount of epinephrin required per day, and the administration of estrogens and androgen, though the patient's response was more striking than such a simple index can show. It seems apparent that either estrogen or androgen under certain conditions could quite markedly decrease epinephrin requirement. A lag of 3 to 4 days occurred when stilbestrol therapy was discontinued before the asthma became worse; similarly when the drug therapy was resumed some days elapsed before improvement was apparent. Since the severity of the asthma was definitely reduced by estrogen it was hoped that larger doses might produce

bleeding continued, and the severity of the asthma remained about the same. No estrogen was given from Nov. 28, 1940 to Dec. 8, 1940, and the patient's condition became much worse. Moreover, on resuming stilbestrol therapy improvement was not as great or as sustained as on previous occasions. The dose was increased on Dec. 25, from 1.0 mg. to 3.0 mg. per day, and relief followed within a few days. With the recurrence of bleeding on Jan. 2, 1941, stilbestrol was stopped and testosterone propionate, 25 mg. every other day, was substituted. It was thought that the androgen would control the asthma equally as well as estrogen by inhibiting pituitary activity, and would allow return of the endometrium to the resting stage, and so permit cessation of bleeding. In the 8 days immediately thereafter, Jan. 3 to 10, but one injection of adrenalin was given, and the patient was more comfortable than at any time since the onset of asthma in

July, 1939. From that time on, however, endocrine therapy gave only slight and fleeting relief, though large doses were used at times. Testosterone propionate, estradiol benzoate and desoxycorticosterone acetate were each tried in large dosage, but they accomplished no more than had stilbestrol. None of these was used for 6 days in April, 1941, and again in

**Adrenals** The right adrenal showed at one pole a friable and degenerating adenoma  $1\frac{1}{2}$  cm. in diameter. The two adrenals together weighed (exclusive of degenerating adenoma) 16 gm. (normal weight 8-14 gm.). Grossly and microscopically they showed areas of considerable hypertrophy in the cortex.

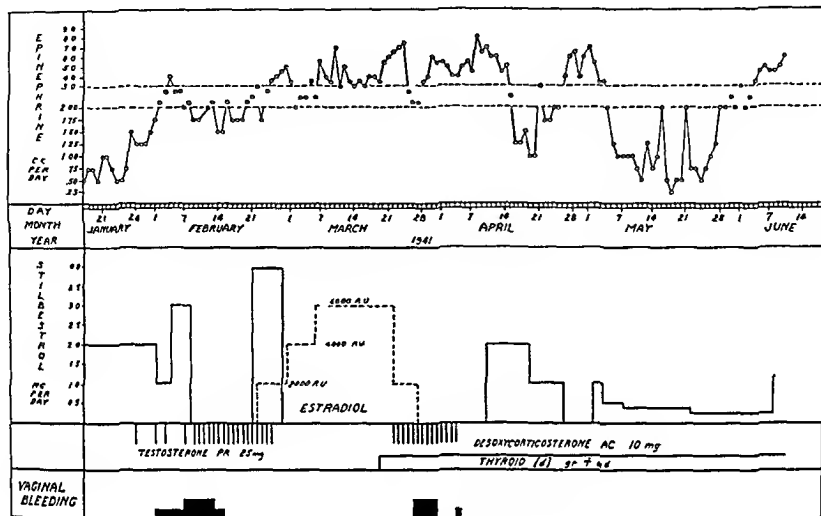


Fig 3 Epinephrine Requirement from January, 1941, to June 12, 1941

May, 1941, and after each of these periods the resumption of stilbestrol was followed by some relief. During May, 1941 the dosage of estrogen was lowered gradually to 0.25 mg per day. In June, 1941 severe status asthmaticus recurred and the patient died on June 12, 1941. Necropsy performed 5 hours post mortem by Dr. A. M. Young showed the following relevant findings.

**Lungs.** These were voluminous, the large and small branches of the bronchial tree throughout were plugged with tenacious greyish white viscid exudate. Microscopically, this exudate showed the arrangement characteristic of Curschmann's spirals and Dietrich's plugs. The walls of the bronchial branches and bronchioles were markedly thickened, in great part due to hypertrophy of the muscular coats, and were richly infiltrated by wandering cells with eosinophiles predominating.

**Liver.** This was of average size and showed no evidence of degenerative change except slight cloudy swelling.

**Ovaries** These showed marked senile involution.

**Uterus** The uterus was small and firm; the endometrium was about 1 mm. in thickness and grossly suggested senile atrophy. Microscopically, however, the appearance of the endometrium was characteristic of an excess estrin-effect with an increase in the size and number of the glands.

**Breasts** Grossly these appeared small and atrophic but on microscopic examination there was considerable increase in the amount of acinar tissue over that expected for the age of the patient.

**Hypophysis** The gland weighed 0.7 gm. Microscopically, the anterior lobe showed slight replacement fibrosis especially in the region of the stalk. The ratio of eosinophilic, basophilic and chromophobic cells was not abnormal.

**Anatomical diagnosis** Chronic and subacute bronchitis and bronchiolitis (marked) with marked mucus plugs in bronchial tree in a case of clinical asthma. Emphysema and fibrosis of the lungs (considerable).



of the menopausal syndrome treated with estrogen, and we believe that these cases also do better on intermittent than on continuous treatment. It occurred to us that long continued inhibition of anterior pituitary function might have resulted in an impairment of adrenal cortical function, and that this in turn might have caused resistance of the pituitary to further inhibition. Blood sodium and potassium levels on March 15, 1941<sup>4</sup> (before desoxycorticosterone had been used) were 373 mg and 18.5 mg respectively, these were normal values.

True asthma (not that resulting from pulmonary or cardiac insufficiency) appearing for the first time in persons over 40 years of age is extremely difficult to control. Experience with this case suggests that pituitary antagonistic therapy may be of help in selected instances. Suitable cases for trial of such treatment would seem to be those in which increased pituitary activity has so altered the activity of the autonomic nervous system as to lower the threshold of allergic reaction. Such cases can probably be selected with some assurance when the reaction makes its first appearance after the occurrence of amenorrhea, the climacteric, in association with hyperthyroidism or diabetes or other manifestation of hyperpituitarism. This means, in general, that the patients amenable to such treatment will be of the older age group. In those allergic patients who have conformed to the more usual pattern by demonstrating clear cut specific reactivity and by responding to environmental change and/or hyposensitization, the true atopic factor is the more important element and any neuro-endocrine disturbance which may be present will probably play a minor rôle.

#### SUMMARY

A case is presented in which bronchial asthma ap-

<sup>4</sup>These determinations were done at the Research Laboratory of Cleveland Clinic through the kindness of Drs. E. P. and Roy McCullagh.

peared under circumstances which suggested that overactivity of the anterior lobe of the pituitary gland was an important factor in its development.

Pituitary-antagonistic endocrine therapy was used with some success.

The possible significance of these observations in relation to the neuro-endocrine atopic mechanism is discussed.

We wish to acknowledge our indebtedness to Robert R. Sanker for the preparation of the chart.

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# Abstracts of

## CURRENT CLINICAL LITERATURE

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### ADRENALS

BALASSA, G., AND M. R. GURD.

Action of adrenalin and potential changes in the cat uterus. *J. Pharmacol. & Exper. Therap.* 72: 63. 1941.

In the anestrus cat uterus spontaneous slow rhythmic potentials occur which are slightly increased by a relaxation due to epinephrin, but abolished by a relaxation due to ephedrine. In estrous or late pregnancy uterine contractions, whether spontaneous or drug induced, are accompanied at the beginning of the contraction by short bursts of spike potentials. These are greatly diminished or abolished in early pregnancy when the reaction to epinephrin is reversed. The authors suggest that the conduction of impulses from cell to cell is a characteristic of the estrous uterus and is responsible for the strong and coordinated contractions which occur during this period. In anestrus uteri such conduction does not occur, and during pro-estrous proliferation it is partially suppressed. The uterine contractions are correspondingly feeble during these phases. Conduction may or may not occur during pregnancy, depending on whether the estrogenic or luteal hormone predominates.—C.P.

HEATH, F. K., G. F. CAHILL AND D. W. ATCHLEY.

Pheochromocytoma—Correct diagnosis and successful operation. *J.A.M.A.* 117: 1258. 1941.

The case history of a patient with a chromaffin tumor of the adrenal gland is presented. The tumor was removed after diagnosis by the perirenal insufflation of air. The postoperative course was entirely satisfactory.—C.P.

THELANDER, H. E., AND M. CHALFFIN.

Neonatal cortical insufficiency (Addison's disease) associated with adreno-genital syndrome. *J. Pediat.* 18: 779. 1941.

A case is reported in a new-born child and the literature reviewed. The symptoms are: a) Those due to acute adrenal insufficiency; loss of appetite, diarrhea, vomiting, weakness, anuria, rapid pulse, cyanosis, extreme dehydration, thirst, high temperature at times and perhaps pigmentation. The child does well on salt and poorly without it. b) Those due to hypersecretion of androgenic tissue. In females, pseudohermaphroditism generally is present at birth while in males hypergenitalism, pubic hair, gruff

voice and advanced bone development appear within a few months. The laboratory findings are those of Addison's disease and high androgen content in the urine. Death occurs in convulsions or coma, in collapse with low temperature or in marasmus. The treatment consists of administration of salt, glucose and cortical extract or D.C.A.—M.B.G. (courtesy Clinical Abstracts).

### ENDOCRINE GENERAL

BONNYCASTLE, D. D., AND J. K. W. FERGUSON.

The action of pitocin and adrenalin on different segments of the rabbit uterus. *J. Pharmacol. & Exper. Therap.* 72: 90. 1941.

The classification of Gunn and Gunn has failed to clarify the observations or to suggest the functional rôle of adrenergic nerves or of epinephrin in uterine motility. The cervical portion of the uterus is relatively insensitive to pituitary extract, but is very sensitive to epinephrin. It is, thus, deduced that the complex action of epinephrin is anti-expulsive and thus physiologically antagonistic to the action of oxytocin.—C.P.

CHRISTIE, U., C. DUNHAM, M. JENSS, AND A. L. DIPPEL.

Development of the center for the cuboid bone in newborn infants. *Am. J. Dis. Child.* 61: 471. 1941.

This is a study of the osseous development of 1,107 newborn—297 white boys, 266 white girls, 268 negro boys and 276 negro girls. Roentgenograms of the infants made within 72 hours of birth showed association of the presence of the center of ossification for the cuboid bone (right side) with race and sex, with certain often used criteria of the maturity of the infant and with the parity and age of the mother.—M.B.G.

DENNIS, W.

Effect of pubertas praecox on the age at which onset of walking occurs. *Am. J. Dis. Child.* 61: 951. 1941.

Reports of cases of pubertas praecox have been examined relative to the age at which healthy infants who attained puberty within the first 2 years began to walk. Data were obtained for 25 cases. The range of ages at which walking began in these cases was from 9 to 18 months, with a mean of 13.58. These figures are substantially the same as those for children of normal growth.

Since pubertas praecox is associated with extraordinary bodily changes in the direction of adult size, proportions and ossification, it must be concluded that none of these developments is the final factor the attainment of which marks the onset of walking —M B G

FREED, S C

Clinical significance of hormone assays *J A M A* 117 103 1941

The studies of hormonal content of urine, blood, and tissues are significant only in relation to clinical history, physical, and other findings of the patient. Definite progress, however, has been made by use of biochemical procedures in determining quantities of certain hormonal substances, especially steroids of ovary, testes, and adrenal cortex. Detailed discussions of the biochemical levels of anterior lobe of pituitary, posterior lobe of pituitary, gonads, adrenal cortex, and pregnancy hormones are given —C P

FREED, S C

Present status of commercial endocrine preparations *J A M A* 117 1175 1941

The commercial hormone preparations are discussed from the standpoint of trade names and potency. The discussion includes estrogens, androgens, progesterone, posterior pituitary preparations, gonadotropins, thyroid, parathyroid and blood Ca raising substances, adrenal cortex, and miscellaneous glandular preparations —C P

KERLEY, C G, AND E J LORENZ

Nutritional obesity in children with private practice *J Pediat* 19 240 1941

The authors report the dietary management of 103 cases of nutritional obesity, in children ranging from 2 to 16 A diet of approximately 1,000 to 1,200 calories with 125 gm of carbohydrate, 75 gm of protein and 35 gm of fat on the average with the addition of Vitamins A, B and D but without glandular therapy resulted in a weight loss of from 3 to 13 lb in from 3 to 16 weeks —M B G

## GONADS

ALBRIEX, A S

Estrogen content of the blood at four hour intervals *Proc Soc Exptl Biol & Med* 47 380 1941

The estrogenic hormone content of the blood of 5 women was determined at 4-hour intervals for one 24 hour period. A significant diurnal rise was noted once, a minor increase in 3 cases and a constant level in one case —L E Gilson (*Courtesy Chem Abstracts*)

ANONYMOUS

Oral androgenic therapy. Current comment *J A M A* 117 622 1941

Methyl testosterone is compared with testosterone. Because of its relatively recent introduction, the only worthwhile indication is the application in treatment of eunuch-

oidism or castration. Other indications must await further investigation —C P

BURLINGAME, C C, AND MARJORIE B PATTERSON

Estrogen therapy in the psychoses *J Nerv & Ment. Dis* 94 265 1941

Estrogen therapy has been employed as part of the treatment program in 139 psychoses. Estradiol benzoate or estrone was employed. The dosage was controlled by vaginal smears, 2,000 to 3,000 R U daily being generally given, intramuscularly, for 30 to 40 days. The most favorable results were obtained in the depressions of the climacterium. Fifty nine per cent of 63 involutional psychoses and 52% of 27 manic depressive psychoses in the depressed phase showed definite improvement, and in some instances recovery, coincident with therapy. The miscellaneous psychoses and the schizophrenia of the involutional period showed no fundamental change associated with this form of therapy —R G H

BURN, J H, AND E R WITHELL

A principle in raspberry leaves which relaxes uterine muscle *Lancet* 1 3 1941.

Experiments are reported showing that dried raspberry leaves contain a principle readily extracted with water which relaxes the smooth muscle of the uterus and intestine when this is in tone. The action is exerted in the body of the cat and also when the muscle is suspended in a bath. The relaxation produced in the body increases with successive doses. The same principle or other causes contraction of the uterus of the rabbit in situ, and also of the isolated uterus of the cat, the rabbit and the guinea pig when these are not in tone. The principle causing relaxation is probably the basis of the traditional use of raspberry tea for making activity in the uterus less painful. A drug which relaxes uterine muscle should be valuable in relieving painful menstruation when this is due to spasmodic contraction of the uterus. The dosage recommended by herbalists is 10 to 20 oz of a 5% infusion of the dried leaves in hot water. This corresponds to 15 to 30 gm of leaf, and judging from the observations in mice, should be entirely non toxic when taken by mouth —*Courtesy Clin Abstracts*

CURRIER, F P, C H FRANTZ AND R VANDER MEER

Reduction of growth rate in gigantism treated with testosterone propionate *J A M A* 117 515 1941

In this case report the male sex hormone has been used as a physiological brake on the growth promoting hormone of the anterior pituitary. Treatment over a 2-year period resulted in a decrease of growth rate when compared to the preceding 2 years —C P

DE TAKATS, G, AND L S HELFRICH

Sterility of the male after sympathectomies *J A M A* 117 20 1941

After extensive removal of the lumbar and thoracic sympathetic chains a patient still had normal spermatozoa,

although 4 months had elapsed since the last operation. This finding contradicts the opinion that such sympathectomies produce sterility in the male.—C.P.

EIDELSBURG, J., AND I. MADOFF.

Effectiveness of methyl testosterone administered orally. *Am. J. M. Sc.* 202: 83. 1941.

Methyl testosterone, administered orally, 100 to 150 mg. per day, was effective in inducing testosterone effects in several different types of patients, all with hypogonadism. Its continued use maintained the effects of testosterone administration. In general, it appears that the earlier changes may be brought about more rapidly by injections of testosterone propionate. All the observations originally made following injections of testosterone propionate in such cases were found in this group with oral administration. Toxic or unusual responses were minimal. None of the patients complained of gastric distress or upsets. The time of dosage or its relation to meals apparently made little, or no difference. The extremes in variation of response may be due to individual case variations or require further study in dose. Methyl testosterone orally appears to be a good, safe, substitutive form of male sex hormone therapy. *Courtesy Clin. Abstracts.*

EIDELSBURG, J., AND E. A. ORNSTEIN.

Observations on the implantation of testosterone pellets. *J.A.M.A.* 117: 1067. 1941.

The authors present 9 case histories all of which indicate that the implantation of pure testosterone tablets offers a means of prolonged androgen therapy. In a series of 30 implants no accident or complication occurred. They now use a bevelled trocar for the implants.—C.P.

FRANK, R. T., AND R. L. BERMAN.

A twenty-four-hour pregnancy test. *Am. J. Obst. & Gynec.* 42: 492. 1941.

An inexpensive pregnancy test requiring only 24 hours (and possibly only 8 hours) is described as being equal in accuracy to the A-Z and Friedman tests. Two female white rats (weight 50 gm.) are each given subcutaneously 5 cc. of fresh first morning urine at 10 A.M. and 4 P.M. and autopsied at 9 A.M. the following day. Ovarian readings are made microscopically and with 10 loupe enlargement by transmitted light. Positive tests have been obtained in 8 hours by the use of 2 four-hourly injections of 5 cc. of urine.—E.C.H.

GRAUER, R. C., C. F. BEALL, AND G. R. WILSON.

Endometrial response to diethylstilbestrol in radium-induced menopause. *Am. J. Path.* 17: 87. 1941.

The endometrial and vaginal response to stilbestrol in 10 radium-treated cases was delayed, and the dose required was greater, as compared to cases of physiological menopause. The stilbestrol produced a proliferative endometrium and stroma which duplicated the appearance of the endometrium before radium was inserted. These

studies confirmed the belief that cases in which an artificial menopause has been produced by radium are more refractory to stilbestrol than cases of surgical sterilization or those associated with normal physiological processes. In the physiological menopausal cases the endometrium remains intact even though it becomes atrophic. In the radium-treated cases we are dealing with the dual effects on the endometrium of the physiological regression incidental to menopause, age, plus the destructive effects of radium.—*Courtesy Clin. Abstracts.*

GREENHILL, J. P., AND S. C. FREED.

The electrolyte therapy of premenstrual distress. *J.A.M.A.* 117: 504. 1941.

The symptoms of premenstrual distress and tension are ascribed to the accumulation of extracellular water and Na retention, which probably results from cyclic ovarian activity. In the brain this may result in headache; in the gastro-intestinal tract distension, nausea, etc. may occur; while in the labia the swelling may cause pruritis. Various methods of treatment are described, but the authors advocate ammonium chloride 3 gm. daily beginning 10 to 12 days before the expected menstrual period.—C.P.

HECKEL, N. J., AND C. R. STEINMETZ.

The effect of female sex hormone on the function of the human testis. *J. Urol.* 46: 319. 1941.

An estrogen ( $\alpha$ -estradiol benzoate) produced sterility in man. It caused a temporary hypertrophy of the male breasts and enlargement of the nipples. Partial impotence developed.—*Authors' summary.*

KLEIN, M. D., AND M. SAROKA.

Studies in viability of human spermatozoa. *Am. J. Obst. & Gynec.* 42: 497. 1941.

A simple method of determining sperm viability, which utilizes methylene blue as an indicator of the absorption of free  $O_2$  is described. The method employed is the following: 1 cc. of spermatic fluid and 1/10 cc. of methylene blue solution are placed in each of 2 ordinary Wassermann tubes and are mixed thoroughly. Each tube is layered with a little heated vaseline. One tube is placed in incubator at 37° C. and the other is kept at room temperature (20° C.). Readings are taken every 15 minutes. Decolorization of the methylene blue results from the utilization of available oxygen by viable sperms. It is presumed that significant relationship exists between decolorization time and sperm viability.—E.C.H.

LEWIS, A. A., AND C. W. TURNER.

Effect of stilbestrol on the mammary gland. *Proc. Amer. Soc. Animal Prod.* 33: 63. 1940.

Stilbestrol was reported to stimulate the growth of mammary ducts, and some lobule-alveolar tissue, but differed from estrogen in having ability in addition to stimulate milk secretion in virgin or dry animals. It did not consistently stimulate glands already in lactation.—G. C. White (*Courtesy Biol. Abstracts*).

tion in relation to the altered menstrual rhythm

The animals used for this purpose must be those which respond in a manner similar to the human female

Thus far, one such animal is the baboon and in the first correlational study (12) it was demonstrated that there is a marked similarity in the way the baboon and the human female react to progesterone. The only salient difference was one of dosage. Since the altered rhythms induced in baboons with progesterone are, generally speaking the same as in women, it follows that any recognizable change in the ovaries of baboons during such experiments most probably find their counterpart in the human ovaries under similar experimental conditions

The present study is the second of such correlational studies between the human female and the baboon but in this instance estradiol benzoate was used instead of progesterone. The results of the investigation in baboons have already appeared (10, 11). Detailed reference will be made to these findings in the body of this paper, but in general it was shown that single injections of adequate amounts of estradiol benzoate in the first part of the cycle produce measurable changes in the size of the perineum and in the length of the menstrual cycle. From this study it was possible to obtain quantitative data on the amounts of estrogen necessary to produce disturbances in the menstrual rhythm

In the present study it is my main purpose to show that single injections of estradiol benzoate given to women in the first part of the cycle can also cause disturbances in the menstrual rhythm. By utilizing the data obtained from baboons an attempt will be made to explain the nature of the menstrual disturbances induced in women. At the same time attention will be drawn to the existence in women of different degrees of sensitivity to estrogen and the technique will be briefly discussed as to how this sensitivity may be recognized clinically

These results, moreover, will be reviewed in order to discover whether they are of any practical value in assessing spontaneous aberrations of the menstrual cycle in women. Finally it is also the purpose of this paper to show the need for elaborating some technique for assisting in prognosticating the tendency towards disease in so-called normal women

#### MATERIAL AND METHODS

The women who subjected themselves to these experiments were unmarried. More than three quarters were under 30 and the remainder were between 30 and 40 years of age. With 4 exceptions each woman had recorded her cycles on a calendar for at least 6 months preceding the experiments. In each

instance intramuscular injections of estradiol benzoate<sup>1</sup> were given on the 8th day of the cycle, counting the onset of menstruation as day one

Each woman formed the subject of a single experiment except one, who was first injected with 1 mg of estradiol benzoate (case 7) and was again treated subsequently with 5 mg of estradiol benzoate (case 6)

#### EXPERIMENTAL RESULTS

*Effect of 5 mg of estradiol (cases 1-6)* On examining table 1 it is evident that 5 mg of estradiol benzoate produced three sets of results. First, in case 1 and 3, the cycle was shortened and bleeding was precipitated 11 days after the injection in case 1 and after 9 days in case 3. Second, the length of the cycle was almost doubled in cases 2 and 4 and third in cases 5 and 6 the cycle was slightly lengthened

It follows therefore that in every case the menstrual rhythm was significantly disturbed by 5 mg of estradiol benzoate

*Effect of 1 mg of estradiol benzoate (cases 7-11)* Again three types of responses were elicited with 1 mg of estradiol benzoate, two of which were similar to those seen after giving 5 mg of estradiol. Two women (cases 8, 9) bled prematurely on the 17th and 19th day of the cycle, i.e., 9 and 11 days respectively after receiving the injection. One woman (case 9) bled again on the 31st day, i.e., she experienced two periods of four days each in the same month and therefore intracyclic bleeding was induced with estradiol in the same way as occurred in some women after progesterone (12) and as Zondek and Rozin (13) reported in all of their experimental cases. In two women the cycle was lengthened (cases 10, 11) but only by 3 days in one instance (case 11). The lengthening in this latter instance could scarcely be regarded as significant. The third type of response (case 7) was negative, i.e., the length of the cycle was unaffected. It was this person who was later injected again but this time with 5 mg of estradiol. Her response to this high dosage was already mentioned (case 6)

With one exception (case 7), and possibly two (case 11) the menstrual cycle was definitely disturbed by 1 mg of estradiol. When the cycle was lengthened it was in no instance as great as that obtained in some women (cases 2, 4) after 5 mg of estradiol. For this reason it was found expedient to give a smaller dose of estradiol in the next series

*Effect of 0.1 mg of estradiol (cases 12-14)* With this lowered amount of estradiol a single woman bled prematurely (case 12) and another definitely (cases 12, 14) and a third (case 13) the cycle was lengthened

<sup>1</sup> The estradiol benzoate supplied by Schering Corporation

Effect of 0.1 mg of estradiol on the menstrual cycle of a single woman

in cases 15 and 16 the length of the cycle was in no way disturbed.

*Effect of 0.01 mg. of estradiol benzoate (cases 23-27).* In none of these five women was there any detectable deviation in the length of the cycle from the normal. It is just possible that all of these women might have been resistant even to 1 mg. of estradiol benzoate as instanced by case 7. This possibility however, cannot be completely excluded especially in view of the

TABLE 1. EFFECT ON THE HUMAN MENSTRUAL CYCLE OF SINGLE INJECTIONS OF ESTRADIOL BENZOATE GIVEN ON THE 8TH DAY OF THE CYCLE

| Case No.       | Amount of estradiol | Length of normal cycle | Length of experimental cycle |
|----------------|---------------------|------------------------|------------------------------|
|                | mg.                 | days                   | days                         |
| 1              | 5                   | 29                     | 19                           |
| 2              | 5                   | 25                     | 45                           |
| 3              | 5                   | 29                     | 17                           |
| 4              | 5                   | 28                     | 44                           |
| 5              | 5                   | 25                     | 31                           |
| 6 <sup>1</sup> | 5                   | 28                     | 36                           |
| 7 <sup>1</sup> | 1                   | 28                     | 28                           |
| 8              | 1                   | 28                     | 17                           |
| 9              | 1                   | 28                     | 19 (31)                      |
| 10             | 1                   | 28                     | 35                           |
| 11             | 1                   | 29                     | 32                           |
| 12             | 0.1                 | 22                     | 27                           |
| 13             | 0.1                 | 29                     | 31                           |
| 14             | 0.1                 | 28                     | 33                           |
| 15             | 0.1                 | 25                     | 25                           |
| 16             | 0.1                 | 27                     | 27                           |
| 17             | 0.5                 | 26                     | 31                           |
| 18             | 0.5                 | 25                     | 31                           |
| 19             | 0.5                 | 23                     | 29                           |
| 20             | 0.5                 | 28                     | 19                           |
| 21             | 0.5                 | 27                     | 16                           |
| 22             | 0.5                 | 26                     | 26                           |
| 23             | 0.01                | 25                     | 25                           |
| 24             | 0.01                | 27                     | 26                           |
| 25             | 0.01                | 28                     | 28                           |
| 26             | 0.01                | 32                     | 33                           |
| 27             | 0.01                | 29                     | 28                           |
| 28             | sesame oil          | 28                     | 27                           |
| 29             | sesame oil          | 28                     | 28                           |
| 30             | sesame oil          | 25                     | 24                           |
| 31             | sesame oil          | 26                     | 27                           |

<sup>1</sup> The same woman. Injected first with 1 mg. (case 7) and later with 5 mg. (case 6).

small size of the group. On examining the results of the previous experiments however, it seems likely that 0.01 mg. of estradiol is incapable of influencing the human menstrual cycle.

*Effect of 0.5 mg. of estradiol benzoate (cases 17-22).* The results of this experiment are shown in table 1, and in general are similar to those found after using 1 mg. of estradiol. Only 1 woman bled prematurely.

*Effect of sesame oil alone (cases 28-31).* It is well

known that some women are easily upset by the slightest emotional disturbance. In order to eliminate the possibility that such a disturbance might have altered the menstrual rhythm in the numerous cases mentioned above, 4 women were injected with pure sesame oil. The cycles of these women were undisturbed. If these results are taken in conjunction with those of cases 23 to 27, it is clear that 9 women were in no way affected as a sequence of the pain experienced during the injection.

#### DISCUSSION

*Disturbance of the menstrual rhythm.* In a previous paper (12) it was shown that the administration of progesterone, either as a single or multiple dose, noticeably influenced the human menstrual cycle. In such instances the cycle may be significantly shortened or lengthened or again intracyclic bleeding may sometimes be induced. In this latter condition despite the premature bleeding menstruation occurs at the normally expected time and two bleedings are therefore experienced in one month.

In baboons single injections of estrogen on the 8th day of the cycle may lengthen the cycle by 10 to 15 days or by 6 to 8 days depending on the amount of estrogen used. In only 1 of 10 baboons was the cycle shortened and in this instance by as much as 12 days (10).

Generally speaking the human female responds to single injections of estradiol benzoate in a fashion similar to that described for the baboon. The length of the cycle may be almost doubled (case 2) or else it may be lengthened by only 3 to 8 days (cases 11, 6). In one woman (case 9) two bleedings occurred in one month, the one 11 days after treatment and the other 3 days later than the normally expected time. In this woman, therefore, intracyclic bleeding was induced in the same way as after progesterone except that after estrogen the premature bleeding took 4 days longer to appear than after progesterone. Although premature bleeding can be consistently induced intracyclic hemorrhage has so far not been produced in the baboon either with estrogen or progestogen.

With the exception of case 9, the cycle succeeding the experimental one was of normal length although in two instances it was shorter by 3 to 5 days than the normal.

*Factors responsible for disturbing the cycle.* In castrate baboons the perineal swelling is completely absorbed. Repeated treatment with estrogen causes the perineum of castrate baboons to swell to enormous dimensions, but when the estrogen is withdrawn the perineum decreases in size until it returns to its resting level. Within 10 to 16 days of the last injection of

estrogen bleeding occurs. Such bleeding is obviously of the estrogen withdrawal variety (10). The deturgescence of the perineum and the latent period of 10 to 16 days after the withdrawal of estrogen in castrate baboons are important factors in facilitating our understanding of what precisely happens when estrogen is injected into normal baboons, without understanding the reactions of normal baboons to estrogen it is impossible to comprehend the nature of the responses seen in women.

By the 8th day of the cycle the perineum of normal baboons is as a rule considerably swollen or turgescient (compare figs. 1 and 2). If to such baboons 1 to 5 mg of estradiol benzoate is administered the perineum increases still further in size for an average of 5 days. Thereafter perineal deturgescence is initiated and it continues until the perineum returns to rest. On an average of 14 days after the injection, turgescence recurs and the perineum then passes through an almost normal rhythm of turgescence, deturgescence and rest. The menstrual cycle in such instances is prolonged by as much as 16 to 20 days.

The fact that the turgescient perineum of these normal baboons underwent deturgescence following the estrogen treatment seemed to suggest that either the production of endogenous estrogen was curtailed or else this exogenous estrogen stimulated the formation of progesterone since either the withdrawal of estrogen or the presence of progesterone can induce deturgescence (14, 15, 16). Examination of the ovaries revealed the absence of any recent corpus luteum, but massive atresia of the large and medium sized Graafian follicles was a characteristic finding (11).

It might be argued that atretic follicles were the source of progesterone and that premature deturgescence was enforced by this hormone. It has been shown, however, that progesterone can induce deturgescence which is maintained for 4 to 7 days only and since the deturgescence produced by estrogen lasted for 10 to 16 days it seems unlikely that the precocious formation of progesterone could have accounted for this prolonged deturgescence of the perineum. On the other hand the atresia of the follicles very strongly suggests that the exogenous estrogen suspended estrogen production by the ovaries by a destruction of the stratum granulosum. The cells of this part of the follicle are usually regarded as being responsible for the elaboration of estrogen. The latent period of 10 to 16 days implies the withdrawal of estrogen. Besides, in normal baboons, treated paradoxically enough with 0.1 mg of estradiol benzoate, deturgescence was prematurely initiated and bleeding supervened 12 days after the injection, i.e., about the same time as occurs before estrogen withdrawal bleeding appears in castrates.

Why estrogen withdrawal bleeding should be precipitated in only 1 of 10 baboons is difficult to explain, but it may be that towards the end of the induced deturgescence in the 9 baboons the ovaries recovered and commenced to elaborate estrogen before the bleeding threshold had been reached. The single baboon which bled might have been sensitive, just as will be described later for women, and the ovarian inhibition was so intense that the endogenous estrogen was elaborated only after the estrogen level had fallen below the bleeding threshold.



FIG. 1. PERINEAL REGION OF AN ADULT BABOON A FEW DAYS BEFORE MENSTRUATION. Note the collapsed lobe (cl), the exposed callosities (ca). This stage is known as perineal rest.

FIG. 2. PERINEAL REGION OF THE SAME BABOON A FEW DAYS BEFORE OVULATION. Note the enormous clitoral lobe (cl) the callosities (ca) are almost covered by the swollen perineum. This stage is known as perineal turgescence.

Small amounts of estradiol (0.1 mg) cause only a partial inhibition of the turgescient perineum which may decrease in size by a few inches and thereafter it returns to its original dimensions to pass through a normal rhythm. The length of the menstrual cycle is increased by 4 to 6 days and this is equivalent to the period during which the perineum was temporarily depressed. In this latter case the injected estrogen produced only a partial inhibition of the ovaries which in turn was responsible for the incomplete perineal deturgescence (11).

In normal baboons, therefore, 1 to 5 mg of estradiol given in the first part of the cycle causes complete perineal deturgescence lasting on an average of 14 days and thereafter the perineum goes through an almost normal rhythm but the cycle is considerably lengthened, whereas 0.1 mg of estradiol leads to partial perineal deturgescence lasting for 4 to 6 days and the cycle is slightly lengthened but in this instance only for 4 to 6 days. Still smaller amounts of estrogen (0.5 mg of estradiol) have a recognizable effect neither on the perineum nor on the length of the cycle.

With these facts before us it is now possible to proceed to analyze the effects of estrogen on the human cycle. Disregarding for the time being the question of susceptibility it is evident that in cases 2 and 4 the cycle was greatly prolonged and in this respect the prolongation can be compared with the reactions of baboons treated with 1 to 5 mg. of estradiol. Naturally, in women it is not possible to watch the day to day progress of events as is possible in baboons. It was especially emphasized that the period of inhibition after estrogen administration in normal baboons is equivalent in length to the latent period which intervenes between the last injection of estrogen into castrates and the onset of withdrawal bleeding. The cycle in baboons is prolonged approximately to the same extent as the period of induced perineal inhibition. It is possible to arrive at an appraisal of the prolonged cycle in women in the same way as in baboons. To achieve this it is necessary to know in castrate women the interval that elapses between the last treatment with estrogen and the onset of withdrawal bleeding.

It is remarkable that despite the numerous occasions on which castrate women have been treated with estrogen so little attention has been devoted to this latent period. It is particularly fortunate that Elden (17) submitted detailed protocols in his experiments in which he attempted to produce a progestational reaction in the endometrium of castrate women. In the three cases reported by Elden the latent period varied from 5 to 9 days. In cases 1, 3, 8, 9, 20, 21 (table 1) bleeding supervened in normal women between 8 days (case 21) and 11 days (cases 1, 9, 20). Combining Elden's figures with those adduced from the present study it seems that the extremes of the latent period lie between 5 and 11 days.

Using case 4 as an example it is now possible to arrive at an assessment of how the cycle was lengthened in women after estrogen treatment.

- a) Duration of the spontaneous cycle before estrogen was injected . . . . . 8 days
- b) Duration of inhibition by estrogen in normal women is equivalent to the length of the latent period before estrogen withdrawal bleeding supervenes . . . . . 5 to 11 days
- c) Total number of days of spontaneous cycle before injection of estrogen plus the duration of inhibition by exogenous estrogen . . . . . 8 + 5 to 11  
= 13 to 19 days
- d) Length of normal cycle . . . . . 28 days
- e) Length of experimental cycle . . . . . 45 days
- f) Difference in length between experimental and normal cycle . . . . . 45 - 28  
= 17 days

It is seen that  $f$  falls within the limits of  $c$ . If case 2 is examined in this manner it will be seen that  $f$  also falls within the limits of  $c$ .

If the above interpretation should prove to be valid it is obvious that a new cycle was initiated without the intervention of bleeding after the period of ovarian inhibition induced by the exogenous estrogen. In other words, the extent of prolongation of the experimental cycle is equivalent to the sum of the number of days the normal cycle progressed before the injection of the estrogen plus the length of time the ovaries were prevented from producing estrogen. The latter is equal to the latent period intervening before estrogen withdrawal bleeding is precipitated in castrate women.

This interpretation receives additional confirmation from the results obtained in cases 1, 3, 8, 9, 20, 21. Bleeding supervened in all of these cases within 8 to 11 days of the injection of the estrogen. The next bleeding occurred with two exceptions at the normally expected interval dating the first day of the new cycle as commencing on the first day of the experimentally induced bleeding. If we add the length of the experimental cycle to the normal we find that in every instance the total length of the two cycles is approximately similar to the experimental cycle of case 2 and 4 (table 1). This is also reflected in table 2.

TABLE 2

| Case No. | Length of normal cycle | Length of experimental cycle | Combined lengths of both cycles |
|----------|------------------------|------------------------------|---------------------------------|
|          | days                   | days                         | days                            |
| 1        | 29                     | 19                           | 48                              |
| 3        | 29                     | 17                           | 46                              |
| 8        | 28                     | 17                           | 45                              |
| 20       | 28                     | 19                           | 47                              |
| 21       | 27                     | 16                           | 43                              |

Case 9 cannot be included as she had 2 shortened cycles.

There can be no doubt that the administration of estrogen produced a profound inhibition of the ovaries and the follicular atresia was probably so extensive that from the time of the administration of the estradiol the ovaries in these women ceased producing estrogen and hence they behaved in a manner identical with that of castrate women who had received a course of estrogen and then the treatment had been suspended. The latent period intervening between the injection of estrogen and the onset of bleeding in the cases quoted above is, if anything, a little longer in some instances than the latent period given by Elden for his castrates. The correspondence is so close that this can scarcely be regarded as fortuitous.

It follows that in cases 2 and 4 the exogenous es-

trogen was adequate to overwhelm almost completely the ovaries and that an almost new cycle was initiated. In those cases which bled prematurely the ovarian inhibition was so profound and the follicular atresia so extensive that by the time the exogenous estrogen had been metabolized the estrogen threshold had fallen so low that withdrawal bleeding occurred and only then was a new cycle initiated.

The greatly prolonged cycle and the much shortened cycle can be regarded as almost identical responses to estrogen except that in the former endogenous estrogen commences to exert its effect before the estrogen has fallen below the threshold value and so bleeding is avoided. Such women may be regarded as having a more stable endocrine balance than those who bled prematurely.

The slightly prolonged cycle experienced by cases 5, 6, 10, 11, 12, 13, 14, 17, 18 and 19, however, require to be considered in a slightly different way. Again this analysis is only possible by considering the behavior of baboons. It has been pointed out that in two baboons treated with 0.1 mg. of estradiol benzoate the turgescence of the perineum undergoes partial deturgescence lasting for 6 to 8 days and therefore the perineum swells once and goes through a normal rhythm except that the cycle is slightly lengthened. In these baboons the ovaries have only been partially inhibited.

Those women with a slightly lengthened cycle have probably reacted in the same way as the two baboons treated with 0.1 mg. of estradiol. The extent of the lengthening of the cycle is obviously related to the degree of ovarian inhibition. Those women who were resistant suffered from very slight inhibition of the ovaries and consequently the cycle was only prolonged by a few days. When the inhibition was more intense the cycle was prolonged by 8 days. The lengthening in such cases then is dependent on the resistance or sensitiveness of women to estrogen. This matter will be more fully dealt with at a later stage in this paper.

In general all types of reactions noticed in baboons can be excited in women, although premature bleeding can be produced frequently in women and rarely in baboons. Although the administration of estrogen to baboons in the first part of the cycle leads to massive follicular atresia this reaction in the ovaries still remains to be demonstrated in women. The effect of estrogen on the human and baboon cycles is so remarkably similar that it is more than likely that the follicles in the human subject also undergo atresia. The conclusive proof for the existence of this atresia in the human female must await histological confirmation.

*Calibration of the estrogen production of the ovaries by means of exogenous estrogen.* It is not possible as

yet to state whether the follicular atresia induced by estrogen in baboons is caused indirectly by inhibiting the pituitary or whether this is due to a direct action by estrogen on the stratum granulosum. Whichever way this exogenous estrogen exerts its effects there can be no question that almost all the follicles undergo atresia.

It is known from studies of other endocrine glands that it is possible to inhibit the action of a gland by administering the specific hormone elaborated by that gland. DeRobertis (18) has demonstrated that a single administration of parathormone leads to a diminution of the volume with retraction of the cytoplasm and hyperchromasy of the nucleus of the cells of the parathyroid gland of the rat. Hydropic degeneration of the parathyroid cells may also occur and this is sometimes associated with the accumulation of colloid substance. Similarly Gersch and Grollman (19) caused the X zone in the mouse suprarenal to disappear by giving small doses of cortical hormone. These investigators are of the opinion that the X zone acts as a reserve tissue which can be depressed when the need for cortical secretion is satisfied in some other way. Gillman and Stein (20) suggested that the cystic corpus luteum which normally forms during the early months of pregnancy in women was due to the retention of secretion, because this was now being elaborated elsewhere. If we accept the thesis that a specific exogenous hormone can cause inhibition of the endocrine gland elaborating that hormone then the fact that estrogen causes the stratum granulosum of the Graafian follicle of the baboon to degenerate affords strong evidence that the stratum granulosum is responsible in part at least for the production of estrogen and conversely that degeneration of the stratum granulosum of all the large follicles is evidence that the production of estrogen by the ovaries is suspended.

Since the inhibition of estrogen formation in the baboon is associated with perineal deturgescence, it follows that if adequate amounts of exogenous estrogen cause complete perineal deturgescence, then it is reasonable to presume that such exogenous estrogen completely inhibited the production of endogenous estrogen. The induction of partial perineal deturgescence on this basis is regarded as resulting from incomplete ovarian inhibition.

In the baboon 1 to 5 mg. of estradiol benzoate caused complete perineal inhibition. For this reason it was suggested that the baboon was producing less than the equivalent of 1 to 5 mg. of estradiol benzoate. Per contra, since 0.1 mg. caused partial deturgescence in 2 baboons and complete deturgescence in a third baboon it was suggested that the ovary was producing just less than, or the equivalent of, 0.1 mg. of



estradiol benzoate, especially as in two additional baboons 0.05 mg. did not visibly effect the size of the perineum nor the length of the menstrual cycle.

By thus calibrating the exogenous estrogen against the endogenous estrogen, using the perineum as an indicator, it was possible to state that the baboon produces almost an equivalent of 0.1 mg. estradiol on the 8th day of the cycle. There is no doubt that the amount of estrogen necessary to inhibit the ovaries can be established for every adult baboon.

In the same manner the amount of estrogen required to inhibit the human ovaries can also be established. It has already been shown that estrogen administered to women in the first part of the cycle can either greatly lengthen the cycle or greatly shorten it or again it may only slightly lengthen the cycle. The first two responses have been regarded as evidence of complete ovarian inhibition, whereas the slightly lengthened cycle was regarded as a partial inhibition.

On this basis therefore it would appear that when the cycle was greatly lengthened or significantly shortened the amount of exogenous estrogen (estradiol) was more than the equivalent of endogenous estrogen, whereas when the cycle was slightly lengthened the endogenous estrogen was almost balanced by the exogenous estradiol benzoate.

From table 1 it is evident that 0.01 mg. of estradiol given on the 8th day did not significantly alter the cycle of any of the 5 women, whereas 0.1 mg. caused a lengthening of 2 days in case 13, and of 5 days in cases 12 and 14, and no effect in cases 15 and 16. It is doubtful whether the lengthening of the cycle in case 13 can be regarded as significant and it is impossible to adduce any other evidence in support of or against this as is so easily possible in the baboon. We can say moreover, that in 2 of 5 women (cases 12 to 16) 0.1 mg. of estradiol benzoate was able to produce partial inhibition of the ovaries, i.e., 3 women were elaborating more than the equivalent of 0.1 mg. of estradiol benzoate whereas 2 women were elaborating almost the equivalent of 0.1 mg. of estradiol benzoate.

When 0.5 mg. of estradiol was injected in 2 women the cycle was significantly shortened (cases 20, 21), in three women the cycle was moderately lengthened (cases 17, 18, 19) and in one woman (case 22) there was no apparent effect on the length of the cycle. This indicates that in some women, the ovary was elaborating less than the equivalent of 0.5 mg. of estradiol benzoate (cases 20, 21), whereas in others (cases 17, 18, 19) it was elaborating almost the equivalent and, in case 22, more than the equivalent, of 0.5 mg. of estradiol benzoate. Further, after 1 mg. of estradiol the cycle of every woman was affected except that of case 7. This woman was later injected

with 5 mg. of estradiol benzoate (case 6) and her cycle was increased in length by 18 days. The experiments on this woman (case 6, 7) illustrate very forcibly the fact that partial inhibition is reflected in a slight lengthening of the cycle. In every one of the 6 cases, the cycle was affected by 5 mg. of estradiol benzoate.

From these experiments it is abundantly evident that by using estradiol benzoate it is possible to disturb the cycle provided that sufficient amounts of the hormone are administered. It is not possible to establish the efficacy or otherwise of a particular quantity of the estradiol to inhibit the ovaries within a few days as in baboons, but that it can be done by carefully watching the length of the cycle, which takes several weeks, there can scarcely be any doubt from the results shown in table 1.

The estrogen formed by the human ovary, therefore, can be calibrated against exogenous estrogen, using the length of the cycle as an indicator. The interpretation of the findings however, involves a consideration of another factor which will be examined seriatim.

*The existence of estrogen-sensitive and estrogen-resistant women.* On closely perusing table 1 it is at once clear that there is a great variation in the resistance or sensitivity of different women to estrogen. Thus one woman will be resistant to as much as 1 mg. of estradiol benzoate (case 7) and yet in another 0.5 mg. not only affects the length of the cycle but actually precipitates premature bleeding (case 21). In some women the cycle may be disturbed by as little as 0.1 mg. of estradiol (case 14). This means that in some women the ovary can resist as much as 1 mg. of estradiol benzoate whereas in others it is sensitive to as little as 0.1 mg. Case 7 is a good example of a resistant type, since after 1 mg. of estradiol benzoate the cycle was unaffected, and when injected later with 5 mg. of estradiol benzoate the cycle was lengthened only by 8 days. The fact that case 5 showed a slight lengthening of the cycle indicates that she too may be regarded as a type resistant to estradiol and that she too might have been refractory to 1 mg. of estradiol. Per contra case 9 may be regarded as a sensitive type because not only was her cycle shortened, but the succeeding cycle also was impaired as she bled 12 days after her induced bleeding. This second bleeding may be regarded as an estrogen withdrawal bleeding and it is unlikely that she ovulated during the month in which she experienced two periods. Similarly, cases 20 and 21 may be regarded as sensitive since 0.5 mg. was able to precipitate bleeding prematurely.

On the basis of whether the cycle is shortened, greatly lengthened, slightly lengthened or unaffected after treatment with estradiol benzoate it is possible

to grade women as very sensitive, sensitive, slightly sensitive or resistant. Thus case 7 can be regarded as an example of type resistant to estrogen, since 1 mg of estradiol did not influence the cycle whereas 5 mg only produced a slight lengthening of the cycle. Case 21, on the other hand, may safely be regarded as being a very sensitive type in that 0.5 mg of estradiol considerably shortened the cycle, whereas case 18 can be classed as slightly sensitive to estrogen and case 14 may be classified as being sensitive or even very sensitive.

The existence of types sensitive to hormones other than estrogen is being steadily established. Hims worth (21) mentions insulin sensitive types, whereas Wilkins, Fleischmann and Block (22) have drawn attention to the prevalence of thyroid sensitive types as measured by the serum cholesterol and the creatinine excretion. It is likely that when techniques are perfected it may be possible to assess the sensitivity to other hormones. So far Gillman (12) has shown that some women are more sensitive to progesterone than others as measured by the effect on the menstrual cycle. The subjective reactions induced with progesterone also indicate that some women have stable autonomic and vasomotor systems, whereas others are unstable as it has been possible to produce a condition simulating premenstrual tension with 30 mg of progesterone in one woman, other women injected with the same quantity of progesterone exhibited no untoward reactions even though their cycles were as profoundly disturbed as the one who experienced violent subjective reactions (23). Frank (24) refers to 'labile' types of women in respect of the subjective reactions experienced by women in the premenstruum.

The evidence presented above indicates that women exhibit different degrees of resistance to estrogen and in this confirms in a factual manner the claims made by many clinicians of the existence of endocrine types. The technique for assessing estrogen sensitivity is simple and will certainly find clinical application.

As with all tests of this character, difficulty arises as to what can be regarded as normal and what are to be the limits of normality. This can only be established after large groups of women are examined. The classification submitted above in respect to estrogen sensitivity is necessarily only arbitrary and will possibly need modification as additional data become available. This study at least demonstrates that women may be resistant or sensitive to estrogen and the suggested technique forms a basis, flimsy though it may be, for arriving at an appreciation of the degree of resistance or sensitivity that women may show towards estrogen.

### *Clinical Significance of Experiments with Estradiol in Women*

*Postponement of the menstrual cycle* Estrogen has been used to postpone the onset of the menstrual cycle. Foss (2) has recommended for this purpose the repeated administration of large quantities of estrogen commencing in the first half of the cycle. There is no doubt that this purpose can be achieved provided adequate quantities of estrogen are used, the exact amount will obviously depend on the degree of sensitivity to estrogen of the women concerned. If the cycle is postponed there seems little doubt that this is achieved by inhibition of the ovaries, and this inhibition is maintained for as long as the estrogen is administered. When treatment is suspended estrogen withdrawal bleeding supervenes after the usual latent period of 5 to 11 days. When enormous doses of estrogen are used hyperestrogen bleeding may be provoked and the object of postponing menstruation is defeated. It is difficult to assess offhand what is an enormous dose of estrogen, because of the varying degrees of individual sensitivity to this hormone. For one woman 0.5 mg may be relatively enormous, whereas for another 5 mg may be scarcely adequate.

If estrogen treatment is continued over a period of several weeks all of the follicles in the ovary may be destroyed as Zondek showed in the human female and a Gillman demonstrated in the baboon. Both of these observations show definitely that exogenous estrogen has a profound effect on the ovary, albeit of a temporary nature.

Of course, if the estrogen metabolism is delicately regulated, estrogen used empirically may have a serious effect. This we have observed clinically when the administration of 1 mg of estradiol benzoate for 7 days actually induced amenorrhoea for several months and during this period there was no evidence of ovarian activity. On the other hand in resistant women large quantities of estrogen may affect the cycle in question, but thereafter the normal menstrual rhythm becomes rapidly established. In baboons 75 mg of estradiol given over a period of 67 days produced scarcely any alteration in the cycle succeeding the experimental one (25). Apparently such huge amounts and even larger may not deleteriously influence subsequent cycles in women (26). These experiments show, then that estrogen given in the first part of the cycle produces ovarian inhibition.

*Intracyclic hemorrhage* Zondek and Rozin (13) induced intermenstrual bleeding in women to whom 50 mg of progesterone had been given. Such bleeding was called "intracyclic bleeding." At about the same time Gillman showed that within 4 to 5 days after the administration of an adequate dose of

progesterone in the first part of the cycle, bleeding could be induced in normal female baboons. In this way the cycle could be shortened by more than half of its normal length. Later it was shown that in women intracyclic hemorrhage could not be consistently produced with progesterone although the cycle could be shortened (12). It was suggested that bleeding in or near the middle of the cycle might be due to a sudden formation of a progestogen attended by an equally sudden diminution thereof (12).

It seems possible now that a sudden increase in the production of estrogen might so inhibit the ovaries as to cause atresia of the follicles attended by a sudden decrease in estrogen and the onset of estrogen withdrawal bleeding some days later. Thereafter the ovary may recover slowly, but only for a few days and since the stimulus for the production of estrogen may be weak, the ovary fails, and consequently bleeding may supervene once more as happened in case 9 where two bleedings occurred within one month.

Mid-cycle hemorrhage may now be due to abnormal progestogen or estrogen metabolism. Apart from the two possible causes of this condition already mentioned, it has been rightly or wrongly suggested on many occasions that such bleeding in the human female and in monkeys near the middle of the cycle may be an indication that ovulation has taken place.

*The prolonged cycle.* It is a common enough experience in clinical gynecology to find women who menstruate normally every 28 days and then for some unknown reason they will experience at 44 to 50-day cycle. Thereafter such women menstruate regularly again. Such a delayed cycle is regarded as a missed cycle. Again there are other women who one month may have a 17 to 19-day cycle and the next a 40 to 50-day cycle. The cause of such disturbances has not hitherto received any satisfactory explanation.

It was shown that a single or a double injection of a total of 20 mg. of progesterone given to women on the 8th day of the cycle is capable of delaying the onset of menstruation for as much as 15 days (12). From this it follows that the sudden production of a progestogenic substance in the first part of the cycle is capable of upsetting the ovarian rhythm sufficiently to delay the onset of menstruation for a considerable time.

Similarly it has been shown that 5 mg. of estradiol benzoate administered on the 8th day of the cycle can delay the onset of menstruation for 16 days (case 4) or even as long as 20 days (case 2). This delay, it is suggested, has been caused by inhibiting the growth of the Graafian follicles for a considerable period and thereafter an almost new cycle is initiated, without the intervention of estrogen withdrawal bleeding.

It is more than likely that in such cases ovulation is postponed and that bleeding does eventually take place from a progestational endometrium.

Where such delayed cycles are encountered in women it might be due either to the prococious elaboration of progestogen as mentioned above or to an excessive formation of estrogen, and this estrogen either directly or indirectly causes follicular atresia which in turn lowers the estrogen threshold for a variable period of time and thereafter the follicles begin to ripen and are able to develop normally. Thenceforth the sequence of events is similar to that which obtains in a normal cycle, except, naturally, that the onset of menstruation is significantly delayed.

The shortened cycle again may be due either to the presence of progestogen as shown in a previous study (12) or else excessive estrogen in a sensitive woman may cause such profound ovarian inhibition that recovery of the follicles is delayed so long that the estrogen falls below the threshold and bleeding is precipitated as described for cases 1, 3, 8, 9, 21 (table 1). In the succeeding cycle it is possible that there may be once more a sudden production of estrogen but in this instance the inhibition is not sufficiently extensive to cause estrogen withdrawal bleeding but adequate partially to inhibit the ovaries and so lead to a slight or excessive prolongation of the cycle. In this fashion a short cycle may alternate with a long one. Examination of the endometrium in the shortened cycle may then show the absence of a progestational reaction but a progestational endometrium will be encountered most probably at the end of a delayed cycle. These experiments with estrogen in women afford valuable information concerning the nature of the mechanism which may lead to aberrations of the normal cycle.

*Estrogen and dysmenorrhea.* Two women (cases 8, 21) normally suffered from severe dysmenorrhea, but they reported that when they bled prematurely following the estrogen treatment such bleeding was unattended by the violent pain which accompanies the normal periods. Since in these two instances the experimentally induced bleeding was most likely of the estrogen withdrawal variety, it seems likely that the dysmenorrhea in these cases must be associated with some abnormality in the progestogen metabolism. While this observation does not in any way materially assist in solving this vexed problem it does at least indicate that temporary relief may be given to some women by the administration of estrogen in the first part of the cycle. To these women even this temporary relief may be most welcome.

*Inhibition of ovulation.* Ball and Hartman (5) have shown that estrogen inhibits ovulation in the *Macacus rhesus*. It has been demonstrated that a

single injection of estrogen also postpones ovulation in the baboon (11). From the experiments reported above it is more than likely that estrogen also postpones ovulation in a number of women especially in those in whom the cycle was significantly lengthened or shortened. That estrogen can inhibit ovulation is evident from the observations of Zondek (1) in the human female and from those of Gillman in the baboon in which the daily treatment with estrogen causes massive atresia of the follicles (11) and even atrophy of the ovary (1). When for some reason it is desirable to inhibit ovulation, there is no doubt that continuous treatment with adequate amounts of estrogen will most certainly achieve this purpose.

*Clinical assessment of the estrogen activity of the ovaries.* Perhaps the most important contribution emerging from this investigation is that it is possible without complicated laboratory procedure to obtain some indication of the functional activity of the ovaries in respect to estrogen. Since the time it was first shown that disturbances in the estrogen metabolism may seriously impair the normal menstrual cycle tireless efforts have been made to discover some method whereby this metabolism of estrogen could be satisfactorily estimated in women with normal and abnormal cycles. To this end the numerous methods for estrogen assay have been introduced. Unfortunately however, the biological assays for estrogen are both tedious and costly, and do not readily allow of their use by clinicians who have no laboratory facilities. What is more important, appraisal of the results of such assays can hardly be possible without accepting the existence of estrogen sensitive and estrogen resistant types of women.

Before such a biological test can be satisfactorily applied it follows that much more information must be made available concerning the range of variation of estrogen levels in so-called normal women. Otherwise a result may be obtained which may be regarded as normal for one woman but which is definitely abnormal for another.

The experiments in women recorded above indicate definitely that some women are more sensitive to estrogen than others. There can be no doubt that there is a measurable difference of the estrogen sensitivity of cases 7 and 9. A careful followup of these two women over the next 10 years may provide extremely interesting information, as it may be possible that these two women may develop different kinds of endocrine disturbances, or one may continue to have normal cycles throughout her life and the other may later develop an abnormal cycle. It seems scarcely credible that such a discrepancy in the reactions to the same amount of exogenous estradiol represents the two extremes of normality. If a sufficiently large

number of women tested with estrogen in the manner indicated can be followed over a number of years and a correlation can be established between the degree of estrogen sensitivity and the susceptibility or resistance to disease it may then become possible to prognosticate the tendency towards disease in so-called normal women. This aspect of gynecology has not yet received sufficient attention but it seems that this approach may yield fruitful results.

#### SUMMARY AND CONCLUSIONS

Estradiol benzoate administered as a single injection to women in the first part of the cycle causes significant alterations in the normal sequence of the menstrual rhythm. Depending on the amount of estradiol and on the sensitivity of each woman, estradiol led to marked shortening of the cycle which was reduced in length by 8 to 11 days, the cycle was greatly lengthened when menstruation was delayed for 16 to 20 days, or, again, the cycle was lengthened by 3 to 8 days.

In one case intracyclic hemorrhage was produced with 1 mg of estradiol such as occurs in some women after treatment with progesterone.

The reactions of the human female to estradiol benzoate are in general similar to those of the baboon under similar experimental conditions, except that in the baboon it has not been possible to induce intracyclic hemorrhage as occurred in one woman, it is also much more difficult to produce a shortened cycle in baboons than in women.

The alterations in the human menstrual rhythm after estradiol are regarded as being due to interference with the normal ovarian rhythm, since in baboons, the administration of estradiol in a single injection causes massive atresia of all the large and medium sized Graafian follicles. Owing to the similar alterations in the cycle of the baboon and woman after estradiol, it is suggested that follicular atresia also occurs in woman.

The greatly shortened and the greatly lengthened cycle in women are regarded as being almost similar reactions, except that in the former, after a period of ovarian inhibition the estrogen threshold is lowered to such an extent that bleeding supervenes, whereas in the latter the ovary recovers before the bleeding threshold is reached and an almost normal cycle follows the inhibited one. The slightly shortened cycle is evidence of partial ovarian inhibition produced in the same way as in baboons.

By using as an indicator the disturbance in the length of the cycle, it is possible to calibrate the production of estrogen by the ovary against known quantities of exogenous estradiol. It is suggested that the much shortened or the much lengthened cycle

after estrogen treatment implies that there is total ovarian inhibition and therefore the amount of estrogen formed by the ovaries is less than the equivalent of the exogenous estrogen.

By grading the responses of women to the same and different amounts of estradiol it has been possible for the first time to present definite evidence for the existence in women of estrogen-sensitive and estrogen-resistant types. This emphasizes once more that every case must be assessed, and that it is impossible to generalize concerning types of grades of response.

On the basis of the facts presented, it is shown that the postponement of menstruation induced by the repeated administration of estrogen commencing in the first part of the cycle is due to ovarian inhibition and that bleeding will occur within 5 to 11 days after cessation of treatment. Such bleeding is regarded as of the estrogen withdrawal variety. The success which attends efforts to postpone menstruation is dependent on the quantity of estrogen used and this in turn is determined by the degree of estrogen-sensitivity of each woman.

Estradiol benzoate used in the manner described can postpone ovulation. It has been shown that intracyclic bleeding may be produced by estrogen as well as progesterone. The causation of intracyclic hemorrhage is briefly discussed.

The problem of the shortened or the prolonged cycle is briefly reviewed and the causation of such cycles is examined in the light of the experimental data presented in this study on women.

Attention is drawn to the technique now available for assessing the estrogen activity of the ovaries and it is suggested that it might be possible by careful

followup to discover whether the estrogen-resistant or estrogen-sensitive types are liable to specific gynecological pathologies.

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# The Nature of the Subjective Reactions Evoked in Women by Progesterone with Special Reference to the Problem of Premenstrual Tension<sup>1</sup>

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## [[Premenstrual Tension]]

IT HAS BEEN KNOWN for many years that emotional states and mental and physical efficiency of women fluctuate very considerably during the menstrual cycle. Ellis (1) has summarized in a masterly fashion the literature relating to this subject. The social implications of these collective observations have not been sufficiently appreciated in regulating the activities of women in industry and in other potentially hazardous occupations. Frank (2) has drawn attention to the severe handicaps experienced by some women in the premenstruum. These may become so grave as to necessitate drastic treatment by temporary or even permanent inactivation of the ovaries. Frank thought that these disturbances were associated with an overproduction of estrogen and its defective excretion. Later Israel (3) tentatively concluded that premenstrual tension was due to defective luteinization or relative hyperestrogenemia and he therefore suggested the use of corpus luteum to alleviate this condition.

In a recent paper it was shown that progesterone administered to women in the first part of the cycle caused significant alterations in the menstrual rhythm, in the same manner as demonstrated in baboons (4, 5). Apart from the disturbances in the cycle evoked during these human experiments, many of these women experienced a variety of subjective reactions simulating so closely those usually encountered before menstruation and even in premenstrual tension that it seemed sufficiently important to merit record

are given in the following short protocols. In table 1 details of the day of the cycle on which the progesterone was administered together with the number of injections, the total amount of progesterone and the effect on the length of the cycle, are briefly summarized.

Cases 1 and 2. These two women experienced no noticeable reactions except that one of them complained of a

TABLE 1. EFFECT OF PROGESTERONE ON THE LENGTH OF THE HUMAN MENSTRUAL CYCLE

| Case No. | Day of cycle injection(s) given | Total amt progesterone | Length of normal cycle | Length of experimental cycle |
|----------|---------------------------------|------------------------|------------------------|------------------------------|
|          |                                 | mg                     | days                   | days                         |
| 1        | 8                               | 10                     | 26                     | 26                           |
| 2        | 8                               | 10                     | 26                     | 32                           |
| 3        | 8                               | 15                     | 29                     | 29                           |
| 4        | 8, 10                           | 15                     | 29                     | 29                           |
| 5        | 8                               | 20                     | 25                     | 13 <sup>1</sup>              |
| 6        | 8                               | 20                     | 31                     | 42                           |
| 7        | 8, 11                           | 20                     | 31                     | 46                           |
| 8        | 8, 12                           | 20                     | 29                     | 29                           |
| 9        | 8, 10                           | 20                     | 30                     | 13                           |
| 10       | 8, 10                           | 20                     | 30                     | 25                           |
| 11       | 9, 11, 13                       | 30                     | 28                     | 17                           |
| 12       | 8, 10, 12                       | 30                     | 25                     | 15 <sup>1</sup>              |
| 13       | 8, 10, 12                       | 30                     | 30                     | 15                           |
| 14       | 8, 10, 12                       | 30                     | 28                     | 16                           |

<sup>1</sup> Intracyclic bleeding

slight 'menstrual pain,' which came on 24 hours after the injection and passed off within a few hours.

Case 3. On the 10th day of the cycle, i.e., 2 days after the injection, she complained of a severe headache and felt very tired. On the 11th day she suffered severe colicky pain low down in the abdomen at which time thick white mucus appeared and lasted for a whole day. Next day severe abdominal pain lasting for 12 hours recurred.

### OBSERVATIONS

The subjective reactions experienced by the women who formed the subjects of this experiment

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Thereafter the patient felt very well and did not have any other symptoms even at the onset of her period.

*Case 4.* Twenty-four hours after the first injection this subject developed an uncomfortable feeling of dryness in the nose similar in many respects to the sensations heralding the common cold. At the same time a severe deep-seated headache developed. On the day of the second injection the patient felt severe pains low down in the abdomen and especially over the sacrum. On the 14th day a thick mucus discharge appeared; this was the first discharge that the patient had ever experienced.

*Case 5.* On the 10th day this patient experienced an interesting group of reactions. These were severe headache, running eyes and nose. The woman said she had developed a cold without any soreness of the upper respiratory passages or the general malaise which is usually associated with that condition. There were violent abdominal pains on the 10th day and these passed off completely a day later. Although she bled twice in the same month (table 1) the second bleeding which occurred near the normal expected time was unattended by the symptoms experienced after the administration of progesterone.

*Case 6.* This individual experienced the worst sensations recorded in this series of experiments. A day after the injection she suffered an attack of faintness associated with a cold sweat, marked dizziness and a feeling of 'blackness' in front of the eyes. She became extremely nauseated and her head ached severely. This ache she described as a feeling as if her 'head were gripped in a vice' and it was relieved only after she fainted. On the 10th day of the cycle her nose became dry and she nearly 'sneezed her head off.' The running nose continued for 2 days but there was no pain. Four days after the injection, although the nose was still secreting freely, she no longer felt any lassitude and her general condition improved rapidly. Although her menstrual bleeding was delayed (table 1) she felt no discomfort.

*Case 7.* This patient experienced nothing abnormal until a day after the second injection when she noticed a thick whitish discharge which lasted for one day.

*Cases 8, 9, 10.* These women said that they felt nothing unusual after the injection.

*Case 11.* The patient developed a very irritable throat on the day of the second injection. She felt 'under the weather' and was extremely irritable, so much so that when teased in the office she threw a pot of ink at her provocateur, a thing she had never done before. During this and the subsequent two days she felt very depressed, very unhappy and had several long spells of weeping. Such depression had never been experienced before and she remarked that it was strange as she was perfectly happy and there did not seem to be any exciting cause. On the day of the third injection she developed severe backache

which passed off when the experimentally induced bleeding set in.

*Cases 12, 13, 14.* These patients had nothing of note to report.

#### DISCUSSION

It is generally accepted that a large number of women experience a varying degree of physical and/or mental incapacity either at or some days preceding the onset of menstruation. Such women as a rule are not sufficiently incapacitated to seek medical advice nor apparently are their daily adjustments of such a complex nature as to precipitate an obvious physical or mental crisis. There are some women moreover who apparently can easily function in an ordinary environment but, when called upon to make a rapid or a spontaneous adjustment during the premenstruum, break down temporarily, sometimes with serious consequences to themselves and even to others.

Whitehead (6) drew attention to a number of serious and fatal accidents among women pilots and later information revealed that many of these accidents occurred at the time when these women were menstruating. Whitehead is of the opinion that there can be no doubt of the relationship between the emotional states and the menstrual cycle. McCance, Luff and Widowson (7) affirmed from their careful examination of a number of women over a period of 6 months that many physical and mental symptoms are obviously and, in some cases, unexpectedly rhythmic; other phenomena show comparatively little periodic variation, whereas many of their results were inexplicable. The symptom-complex described by Frank and called premenstrual tension manifests itself 7 to 10 days before the onset of menstruation in the form of marked physical unrest, great irritability and a desire to find relief by foolish and ill-considered actions. The existence of this clinical condition was later confirmed by Israel.

The etiology of the physical and mental disturbances immediately preceding menstruation is not definitely known. Frank was the first to suggest a hormonal pathogenesis for premenstrual tension. In 'labile' women the excretion of estrogen does not proceed in a normal manner, and in the premenstruum the concentration of the female sex hormone affects the sympathetic and the cardiovascular systems to the extent expressed by the symptoms. On the first day of menstruation Israel (3) curetted 3 of 4 women suffering from premenstrual tension. He found two to be bleeding from an interval and one from a hyperplastic endometrium. In his opinion this seemed to indicate that cyclical bleeding was taking place from an endometrium lacking the secretory influence of the

corpus luteum and therefore either ovulation had failed to take place or else there was a quantitative disproportion in the production of the ovarian estrogen and progesterone. Israel felt in consequence of the histological examination of the endometria in his 3 cases, that premenstrual tension was most probably due to defective corpus luteum activity and that it was plausible to treat such cases with progesterone.

In the experiments recorded above it was seen that in one woman (*case 11*) the administration of 30 mg of progesterone in the first part of the cycle produced a profound mental effect, almost simulating the picture of premenstrual tension, even to the extent of being dramatically relieved when the uterine bleeding appeared, although in this instance it was precipitated prematurely on the 17th day of the cycle (table 1, *case 11*). Israel's suggestion that premenstrual tension might be due to defective corpus luteum activity receives support from the reactions of *case 11* here reported, but it is hardly likely that it is due to a deficiency. That it is plausible to treat cases of premenstrual tension with progesterone scarcely seems logical, nor is this remark supported by Israel's results in 10 cases, as the administration of corpus luteum cured one and temporarily relieved six, four of the six and two additional patients were subsequently cured by low dose irradiation to the pituitary gland and the ovaries, one malnourished patient was benefited by a gain in weight aided by insulin therapy. This does not seem to be an impressive basis for inspiring the continued use of progesterone in alleviating premenstrual tension.

Apart from the severe mental effect induced in *case 11*, progesterone was responsible for a variety of other symptoms in this and other cases. These and their incidence are shown in table 2.

On analyzing the symptoms (table 2) it is noteworthy that the nose should have been so frequently implicated. This coincidence can hardly be regarded as cogent evidence for the existence of a nasogenital relationship but the possibility cannot be entirely disregarded. On the other hand such reactions may be caused quite easily by a disturbance in the vasomotor mechanism. Of those who complained of headache one patient in particular was of special interest. In this instance (*case 6*) the description of the headache was so unmistakable as to leave little doubt that the pituitary had been affected.

The low abdominal pain, backache, irritability, fainting attacks and vertigo are symptoms which cannot escape emphasis especially as the women were certain that these reactions were never previously experienced in the first part of the cycle. Even before the onset of the normal menstruation those women who complained of those symptoms stated very defi-

nately that the reactions were never so severe as those induced experimentally. The fainting attack was the first ever experienced by *case 6*.

On comparing these symptoms with those commonly appearing in the premenstruum, it is at once apparent that they are strikingly similar. Both apparently are probably disturbances of the vasomotor mechanism and of the vegetative nervous system. In the experimental subjects the onset of these symp-

TABLE 2 SYMPTOMS EXCITED IN WOMEN TREATED WITH PROGESTERONE IN THE FIRST PART OF THE CYCLE<sup>1</sup>

| Symptom                     | Frequency |
|-----------------------------|-----------|
| Rhinorrhoea                 | 5         |
| Low abdominal pain          | 4         |
| Headache                    | 3         |
| Melancholia                 | 2         |
| Profuse cervical discharge  | 2         |
| Irritation of the throat    | 2         |
| Backache                    | 2         |
| Irritability and depression | 1         |
| Fainting attack             | 1         |
| Vertigo                     | 1         |

<sup>1</sup> Seven women experienced no reactions at all even though in some cases the cycle was profoundly disturbed.

toms within a day or two after the administration of the progesterone and their sudden disappearance at a time when this hormone has been metabolized affords undeniable evidence that progesterone in sufficient concentration is the exciting cause. Since the menstrual moulins usually disappears with the onset of menstruation or soon after it is suggestive of the possible rôle of progesterone in their production. Obviously progesterone alone is not the only factor as 7 of the 14 women were unaffected.

Frank felt that in premenstrual tension not only was a particular disturbance in the secretion of the ovarian hormones necessary, but also that this must take place in a 'labile' woman. Although 'labile' is not a happy term it nevertheless implies that there are women who are much more easily upset by slight deviations from normal activity of the ovaries than others. This is clearly demonstrated in the above experiments with progesterone and experiments of a similar nature with estradiol benzoate (8) go to prove the same point. It follows that the symptomatic responses to progesterone will depend on the degree of sensitiveness of the nervous system of each woman to this hormone. Some women will be profoundly affected by a relatively small dose, whereas others even after very large doses feel no ill effects.

This variation in the susceptibility of the nervous system to hormones in supposedly normal women is obviously important, but the knowledge is somewhat lessened in the absence of sufficiently reliable tech-



tics for assessing this stability in each woman. The assay of the ovarian hormones or their derivations in blood and urine is obviously an important step in that direction, but quantitative assays (at present a laborious process) so far alone have not proved to be as valuable as anticipated since there are a host of unknown problems in connection with the metabolism of the hormones and the state of the nervous system which do not allow of a satisfactory interpretation of the findings. In the meantime it seems that the judicious and controlled administration of hormones in one or other part of the cycle together with a careful follow-up of the reactions elicited may afford some indication, crude as it may be, of the degree of sensitiveness of the nervous system. For example, if we examine the effects of 30 mg. of progesterone (*cases 11, 12, 13, 14*, table 1) we see that the subjective reactions in *case 11* were very severe, whereas in the others they were not sufficiently marked to merit any attention. Although *case 11* in ordinary circumstances can be regarded as normal it is quite obvious that if here endocrine balance should become disturbed by an abnormal production of progestogen she might be destined to suffer from premenstrual tension. Such a woman employed in a dangerous occupation (pilot, industrial worker) under certain circumstances outside her control, may become a menace to herself and even to others.

It is evident, moreover, that a disturbed menstrual cycle is not necessarily attended by symptomatic reactions, as in *cases 11, 12, 13, 14* the menstrual cycles were altered in more or less the same fashion and yet *case 11* was the only one to experience severe reactions; the others were completely unresponsive. Again, the severity of the symptoms or even their presence is not dependent on the amount of progesterone since 30 mg. progesterone excited no reactions in *case 12, 13, 14*, whereas 15 mg. was able to incapacitate a woman by causing a severe headache and violent abdominal pains (*case 4*). Just as it was shown in a previous investigation that women vary considerably in their ability to prevent progesterone from upset-

ting their menstrual rhythm (5), so too, it transpires, that women vary considerably in the way they react subjectively to the same hormone. There is thus a considerable fluctuation both in the stability of the endocrine balance and in the sensitiveness of the vegetative nervous system of different women although it may be constant in each woman. A thorough appreciation of this variability is of the utmost importance, for on this depends, not only the manner in which we treat aberrations of the menstrual cycle, but also, the extent to which we shall be able to prognosticate the tendency towards disease of so-called normal women.

#### SUMMARY

By using progesterone it has been possible in the first part of the cycle to produce in one woman a condition simulating premenstrual tension and in others reactions similar to those encountered in the premenstruum.

The subjective reactions elicited are not necessarily associated with disturbances of the menstrual rhythm and vice versa.

Not all women are affected in the same way by progesterone, nor is the extent of the reaction dependent on dosage.

The appreciation of the existence of individual sensitivity to hormones is of the utmost importance in determining treatment of menstrual disturbances and in the prognostication of the tendency towards disease in so-called normal women.

I wish to record my thanks to Professor Raymond A. Dart for his advice and encouragement.

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# A Six-hour Pregnancy Test

## [Chorionic Gonadotropin]

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THE WORK REPORTED HERE had its origin in a series of studies designed to determine how soon after the administration of gonadotropic hormone, gonadotropic effects could be detected in the immature rat ovary. In a study of the time factor relationship of follicle stimulation to luteinization in the immature rat, several years ago, it was noted that "in some cases the immature rat ovary will respond to gonadotropic hormone with a follicle stimulating reaction as early as 26 hours after the first injection" (1). In subsequent studies an attempt was made to determine whether it was possible, by increasing the dosage of the gonadotropin, adding hypophyseal synergist or using older animals, to accelerate the gonadotropic action of the extracts. Two observations were made during these studies which suggested their utilization as a test for human pregnancy. These observations are that, a), as early as 6 hours after the administration of pregnancy urine to immature rats, one can detect marked hyperemia of the ovaries, and, b), by the end of 24 hours one can discern gross and microscopic evidence of estrogenic stimulation of the vagina. It was felt that these reactions which are evoked respectively by the gonadotropic and estrogenic hormones present in pregnancy urine could serve as a rapid dual test for pregnancy, providing for a reading in 6 hours and a supplementary check at the end of 24 hours. To be of practical value as a test, the end points of these reactions must be easily detectable grossly and consistent in their occurrence.

In order to determine if such end points could be established, a preliminary series of experiments was performed with urines of normal pregnancies and control urines from nonpregnant individuals. The effects upon the ovaries, uterus and vaginae were studied grossly and microscopically at intervals of 6, 12, 18 and 24 hours after injection. The amount of urine administered varied from 1 to 8 cc and the animals used varied in weight from 30 to 52 gm. These preliminary studies revealed that at the end of 24 hours the two reactions, ovarian hyperemia and hyper-

trophy of the vagina, were clearly detectable by the naked eye, but at shorter time intervals, the estrogenic action on the vagina became progressively less marked so that below 12 hours it was not possible to detect gross evidence of the estrogenic effect. The ovarian hyperemia however, was uniformly detectable as early as 6 hours after the injection and in some instances was more striking at 6 than at 12 or 24 hours. It was noted furthermore that varying the dose from 1 to 8-cc did not appreciably affect the reactions and that variations in weight of the animals from 30 to 52 gm did not significantly influence either the ovarian or vaginal reactions.

To determine the reliability of these reactions as a test for human pregnancy, we have performed a series of tests of unknowns, comprising urine specimens from women in various stages of pregnancy, as well as from menopausal, amenorrheic and normal cyclical women. The urines were tested by both the 6 hour ovarian reaction and by the 24 hour ovarian and vaginal reactions.

### METHODS AND MATERIALS

**6 hour test.** For the 6 hour test, three immature rats (wt 35-45 gm, ages 22-25 days) were each injected subcutaneously with 2 cc of the night specimen of urine and autopsied at the end of 6 hours.

**6 hour ovarian reaction.** The ovaries were enlarged and bright red in appearance in sharp contrast to the small, white or faintly pink ovaries of the control animals. Microscopic examination of the ovaries at 6 hours revealed in the majority, perfollicular zones of vaso dilatation and diffuse hyperemia of the parenchyma of the ovary (fig 1, 2). Not infrequently, microscopic examination of fixed and stained sections failed to reveal the vaso dilatation in ovaries which, in situ, were observed to be markedly hyperemic. This discrepancy is in part probably attributable to the formalin and alcohol fixation and in part to disruption of the ovarian capsule, the dilated vessels of which contributed to the grossly visible red appearance of the ovaries.

**24 hour test.** Two immature albino rats (wt 35-

45 gm.) were given a single subcutaneous injection of 2 cc. of the urine to be tested and the animals autopsied at the end of 24 hours.

**24-hour ovarian reaction.** Ovaries of animals autopsied 24 hours after the administration of 2 cc. of pregnancy urine showed a characteristic gross reaction of vascular congestion essentially similar to that observed at the end of 6 hours.<sup>1</sup> Serial sections of the 24-hour ovaries revealed varying degrees of perifollicular and hilar vaso-dilatation.

pregnancy varying from approximately 18 to 280 days), one from a patient with chorioepithelioma and 31 from nonpregnant sources (instances of cyclical menstruation, primary and secondary amenorrhea, menopause, functional sterility with delayed menstrual periods, adrenal cortex carcinoma and normal males) were used. With but one exception, all of the tests performed on the urine from various stages of pregnancy and from the chorio-epithelioma case were read as positive. The one exception was a negative

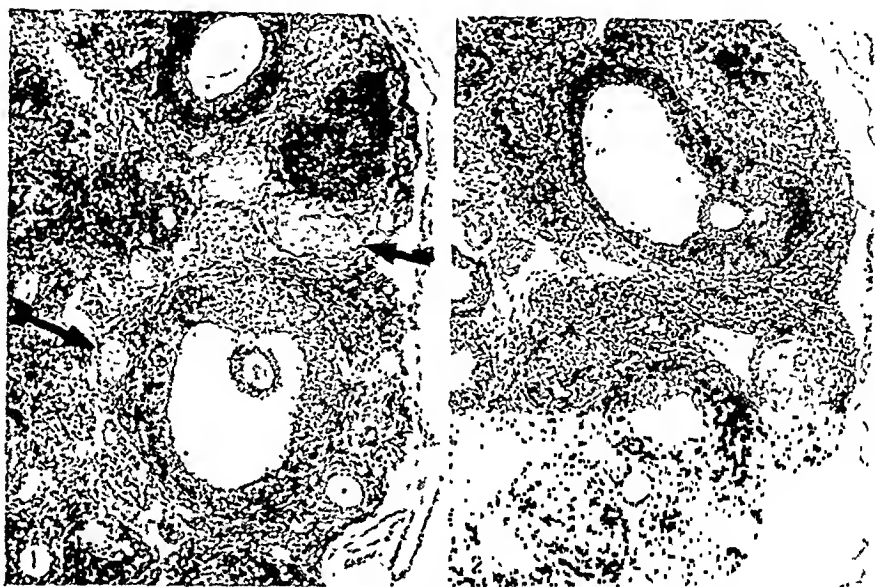


FIG. 1. SECTION OF OVARY OF IMMATURE RAT (wt. 35 gm.) 6 hours after injection of 2 cc. of pregnancy urine, showing perifollicular vascular dilatation.  $\times 70$ .

FIG. 2. SECTION OF OVARY OF CONTROL RAT 6 hours after injection of 2 cc. of urine from nonpregnant cyclical woman. Note absence of hyperemia.  $\times 70$ .

**24-hour vaginal reaction.** The vaginae of animals examined 24 hours after the injection of pregnancy urine were noticeably thicker and broader than those of the controls. Naked eye recognition of the vaginal hypertrophy is easily accomplished as soon as one familiarizes oneself with the difference in gross appearance of the excised vaginae of the positive and control animals. Microscopic examination of sections of the vaginae revealed that the increased thickness of the vagina was due to proliferation of the vaginal epithelium and hypertrophy and edema of the muscularis (fig. 3, 4.)

#### Tests of Unknown Urines

**Results of 6-hour tests.** One hundred and ten urine specimens 78 from pregnant women (the length of

reading made on the urine of a patient 5 days after the date of her expected period. The test was repeated one week later and found to be strongly positive. The subsequent clinical course confirmed the diagnosis of pregnancy. Of 234 animals injected with pregnancy urine, 8 showed borderline reactions. In each instance, however, the mates injected with the same specimen had strongly positive reactions. All of the 31 tests performed on urine from nonpregnant sources (except for the chorio-epithelioma cases) were read as negative.

**Results of 24-hour tests.** The urine specimens tested consisted of 61 obtained from women in whom pregnancy was subsequently verified clinically, and 57 from nonpregnant women comprising normal cyclical, menopausal, ovariectomized and amenorrheic women. Of the 118 unknowns tested, at the end of 24 hours the gross ovarian and vaginal reactions conformed to the clinical diagnosis in all but two instances. The two exceptions were a false negative ovarian and vaginal reaction obtained in a very early pregnancy

<sup>1</sup> Recently, Frank and Berman (2) have reported similar observations. These authors employed 2 injections of 5 cc. of urine, 6 hours apart, into each of 2 rats weighing 50 grams. For the reading, they recommend examination of the ovary by transmitted light with the aid of a lucite rod, using 10 loupe magnification, 24 hours after the first injection.

(4 days after the expected period) and a false ovarian negative with positive vaginal reaction in a late pregnancy (10 days before term). In the first instance, a repetition of the test, several days later, resulted in a dual positive reaction and, in the second, the ovarian reaction was equivocal in the repeated test and the vaginal reaction remained positive. Microscopic examination of the latter ovaries failed to reveal more than a slight degree of congestion, whereas the vaginae showed striking evidence of estrogenic stimulation in both the epithelial and muscular coats. The negative ovarian reaction is probably attributable to the low concentration of gonadotropin present in this advanced stage of pregnancy, whereas estrogenic hormone was present in sufficiently high concentration to evoke the characteristic vaginal reaction.

#### DISCUSSION

It appears from this study that the administration of human pregnancy urine to immature female rats results in marked hyperemia of the ovaries which is grossly visible 6 hours after the injection. That this vascular reaction is due to the gonadotropic factor present in pregnancy urine was shown by the production of a similar vascular reaction with chorionic gonadotropin<sup>2</sup> and by the failure to induce the reaction with pregnancy urine, in which the gonadotropin had been inactivated by boiling. This study has revealed, furthermore, that the urine of pregnant women contains estrogens in such high concentration, that administration of 2 cc of urine to an immature rat causes proliferation of the epithelial and muscular coats of the vagina, which is detectable microscopically and grossly, 24 hours after the injection. The proliferative changes in the vaginal mucosa are identical with those induced by estrogens. It is interesting in this connection, to recall that Allen, Smith and Gardner (3, 4) have reported a proliferative reaction in the vaginal mucosa of ovariectomized adult mice 9½ hours after the administration of estrone and colchicine and suggested this reaction as a test for estrogen. We have found microscopic evidence of epithelial proliferation as early as 6 hours after the administration of pregnancy urine and colchicine but, since these changes could not be detected grossly, they are of no practical value as a test for pregnancy. At 24 hours, however, the vaginal reaction appears to be as reliable an indicator of human pregnancy as the ovarian vascular reaction.

That the vaginal reaction is attributable to the estrogens present in the urine and is not mediated through the ovaries was shown by the induction of epithelial proliferation in the vaginae of immature

rats with pregnancy urine in which the gonadotropin had been inactivated by boiling and also by the fact that a similar vaginal reaction was induced with pregnancy urine in immature ovariectomized rats. Neither the ovarian nor the vaginal effects have been produced by comparable amounts of the urine of normal cyclical women or by the gonadotropin-containing urine of ovariectomized women or women



FIG 3. CROSS SECTION OF PART OF THE VAGINA OF AN IMMATURE RAT (wt. 36 gm) 24 hours after the injection of 2 cc of pregnancy urine. Note the marked proliferation of the epithelial cells and increased thickness of the muscularis.  $\times 45$

FIG 4. CONTROL CROSS SECTION OF PART OF THE VAGINA OF AN IMMATURE RAT (wt. 35 gm) 24 hours after the injection of 2 cc of urine from a normal cyclical woman.  $\times 45$

with functional amenorrhea or the menopause syndrome.

Although the series of unknowns tested at 6 hours is rather small, the results have been sufficiently consistent to merit recommending it as a simple, rapid and comparatively inexpensive test for human pregnancy. If, for some reason, it is inconvenient to examine the ovaries at 6 hours, the animals may be autopsied at any time during the following 24 hours. Since the end-point of the test consists of hyperemia of the ovaries, it is imperative that the ovaries be examined immediately after death. It has been our practice to asphyxiate the animals with illuminating gas. In performing the autopsy, it is, furthermore, important to avoid injuring vessels in the abdominal wall, since blood in the abdomen makes it difficult to detect the ovarian hyperemia.

The 6 hour test described here has the advantage of being more rapid and less costly than the Ashheim-Zondek test which is performed on 5 mice and takes 96 hours, and the Friedman test which gives the most accurate results when performed on 2 rabbits and requires 48 hours (5).

We have found it most convenient to inject the animals at 10 A.M. and perform the autopsies at 4 P.M. It is important for those planning to use this

<sup>2</sup> The chorionic gonadotropin (Pranturon) was a product of Schering Corporation, Bloomfield, New Jersey.

test to become familiar with the normal gross appearance of the ovaries of immature rats. It is advisable to start with a series of known pregnancy urine specimens and to contrast these ovarian reactions with those induced by negative urines before attempting to obtain readings of unknowns for diagnostic purposes.

#### SUMMARY AND CONCLUSIONS

A 6-hour test for human pregnancy is described, based on the observation that the chorionic gonadotropin causes a marked hyperemia of the ovaries of immature rats, which is grossly discernible 6 hours after the injection. For the performance of this test it is recommended that three animals (wt. 35-45 gm.) be each injected with 2 cc. of the first morning specimen and autopsied at the end of 6 hours. Positive results were obtained in all but one of 78 tests of preg-

nancy urines and negative results in all of the 31 tests of urine specimens from nonpregnant individuals.

A confirmatory 24-hour test is also described which is based on the proliferation of the epithelial and muscular elements of the immature rat vagina induced by the estrogens present in the pregnancy urine. Confirmation by the 24-hour vaginal reaction is unnecessary as soon as one becomes familiar with the 6-hour ovarian vascular reaction.

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# On the Mechanism of Insulin Resistance in Toxemic States<sup>1</sup>

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## [Carbohydrate Metabolism]

IT IS WELL known that the early stages of toxemia, from whatever cause, may be accompanied by hyperglycemia, glycosuria, and a diminished carbohydrate tolerance as indicated by the dextrose tolerance test (1, 2). The response to a given dose of insulin is less than that in the normal individual (3). Diabetic patients who were formerly well controlled by a small dose of insulin may, with the advent of toxemia, be poorly controlled even with very large insulin dosages (4). This condition has been commonly referred to as 'insulin resistance'.

Previous work has clearly shown that the liver is a major factor in determining carbohydrate tolerance (5). It has also been demonstrated that liver damage by toxins diminishes carbohydrate tolerance by interfering with the homeostatic mechanism for the maintenance of the constant normal blood sugar level (6, 7). Since insulin is an important regulator of this hepatic mechanism, it was logical to seek the cause of insulin resistance in the liver.

Our knowledge of the chemical steps involved in the buildup and breakdown of liver glycogen has undergone a radical change within recent years. It was formerly thought that hepatic glycogenolysis normally occurred through amylase activity, the glycogen being degraded through dextrins to maltose and to glucose (fig. 1). However, Lee and Richter (8) who recently summarized the previous work on liver amylase and reported their own thorough studies on the subject, pointed out that a), even the highest amylase activity found in the blood, liver and other organs is only of the order of 1/10,000 of the amylase activity of the pancreas, b), the small amounts of amylase found in the liver and other organs may be regarded as traces of the very active pancreatic and salivary amylases which have diffused into the blood and throughout the system, and c), the amylase present in the liver probably exerts little or no activity *in vivo*, because of the absence of a sufficient concentration of free chloride ions within the hepatic cells.

They concluded that the amylase found in the liver is not concerned in any normal hyperglycemic mechanism. More recently Somogyi (9) has analyzed the carbohydrates present in normal liver and has found only glycogen and dextrose, with no trace of maltose or other nonfermentable reducing substance such as would result from amylase activity. Since he has never been able, by any method to extract more amylase from the liver than would correspond to the enzyme

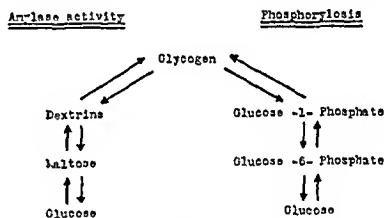


Fig. 1

content of the extracellular fluid, Somogyi has concluded that the hepatic cells contain no amylase whatever.

On the other hand, the work of Parns (10), Cori (11, 12) and Ostern and Holmes (13) has been generally recognized as demonstrating that the steps between glycogen and glucose in the liver are mediated by phosphorylating mechanisms (fig. 1). It has been shown that the rates of these transformations are sufficiently rapid to account for even the most intense forms of hyperglycemia encountered *in vivo*. It is presumably upon these or related phosphorylations that insulin exerts its regulatory influence (14), although its exact point of action is still unknown.

Whether or not some small amount of inactive amylase is normally present within the hepatic cells, it occurred to us that in the liver damaged by toxins the normal barrier which excludes amylase or the normal environment which inhibits amylase activity might be disturbed. In either case liver glycogen would then be broken down through this abnormal

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pathway, as well as by phosphorylosis. Since only the normal portion of the combined glycogenolysis would be subject to control by insulin, this could account for the socalled insulin resistance. The experimental data to be presented supports this hypothesis.

METHODS

The study of the hepatic enzyme activities before and after the influence of toxin necessitated the re-

TABLE I. INFLUENCE OF DIPHTHERIA TOXIN ON LIVER GLYCOGEN IN VIVO

| Glycogen before injection | Time after toxin injection | Glycogen after injection |
|---------------------------|----------------------------|--------------------------|
| gm. %                     | hr.                        | gm. %                    |
| 6.46                      | 3.5                        | 1.85                     |
| 5.47                      | 3.5                        | 1.41                     |
| 5.25                      | 4.0                        | 1.28                     |
| 5.14                      | 3.0                        | 2.63                     |
| 4.28                      | 2.5                        | 1.38                     |
| 3.53                      | 3.5                        | 1.07                     |
| 3.40                      | 3.5                        | 0.37                     |
| 3.31                      | 3.0                        | 0.90                     |
| 3.10                      | 3.5                        | 0.30                     |
| 2.16                      | 2.0                        | 1.19                     |
| 1.98                      | 3.0                        | 0.39                     |
| 0.60                      | 3.0                        | 0.07                     |
| 0.59                      | 2.5                        | 0.31                     |

peated sampling of the liver from the same living animal; this work was done on dogs under nembutal anesthesia. It was necessary to quickly wash the liver samples as free as possible from blood, because of the

through a large needle inserted into the distally occluded portal vein) and immediately removed, it was substantially free from blood and blood amylase, as judged by the negligible rate of glycogenolysis in a phosphate-free medium. This procedure, however, was not suitable for our work since we wished to compare the enzyme activity of samples of the same liver before and after the influence of toxin. We were fortunately able to accomplish the same result by removing small samples of tissue from the intact organ and immediately washing them under a strong current of cold tap water. Although the latter procedure might conceivably wash out some of the small amount of amylase which may be present in the liver cells both the control samples and those obtained after treatment with toxin were treated in the same manner, and the results should be comparable. All of the determinations of enzyme activity referred to below were therefore made on liver samples which had been washed free from blood amylase in this way.

The general experimental procedure was as follows. A laparotomy was performed on the anesthetized normal animal and a sample of liver was excised for control determinations. One portion of the sample was immediately frozen in carbon dioxide ice and used for the determination of the initial values of total carbohydrates, glycogen, free sugar, organic and inorganic phosphates. Another portion was washed, minced and used for the determination of glycogenolytic activity. Meanwhile the animal's

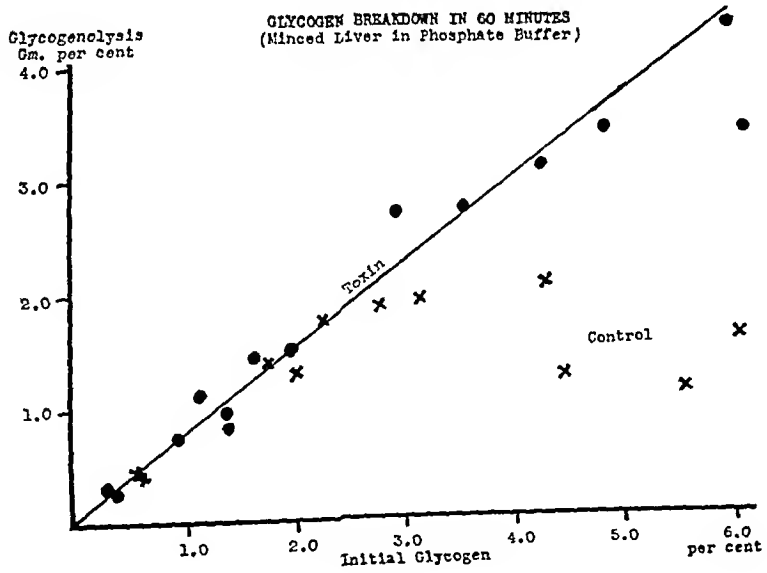


Fig. 2

probability that the altered membrane permeability of the excised liver cells would soon allow the relatively large amounts of blood amylase to enter. In preliminary experiments it was found that when the liver was washed in vivo, (with cold tap water,

abdomen had been closed and 100 to 180 M.L.D. of diphtheria toxin<sup>2</sup> per kg. of body weight had been injected intravenously. Two to 4 hours later addi-

<sup>2</sup> We are indebted to Eli Lilly & Company of Indianapolis, Indiana, for a supply of standardized potent diphtheria toxin.

tional samples of the liver were taken and the above determinations repeated. The type and amount of toxin used had been shown to effect carbohydrate tolerance significantly within the specified period in previous experiments under comparable conditions (6, 7).

The total carbohydrates were determined by the method of Benoy and Elliot (15). The free reducing substances, referred to as 'free sugar' for the sake of brevity, were estimated by the same method, omitting hydrolysis in acid. The glycogen was determined by the method of Good, Kramer and Somogyi (16). The analysis for inorganic phosphate was made by the procedure of Fiske and Subbarow (17), the hexose phosphate content was calculated from the P value after hydrolysis for 100 minutes in  $\text{HCl}^3$  (18, 19).

### RESULTS

Table 1 summarizes the data on the initial glycogen content of liver samples removed before and after the

genolysis proportional to their initial glycogen levels, when the latter were low. However, above levels of 20 to 25 per cent initial glycogen which is within the usual normal range, the rate of glycogenolysis no longer increased with the initial glycogen level, but remained more or less stationary at a rate of 20 gm per cent per hour or less. In sharp contrast to this, the samples of liver removed after toxin administration showed rates of glycogenolysis proportional to the

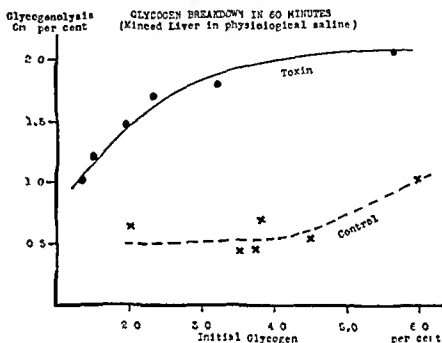


Fig 4

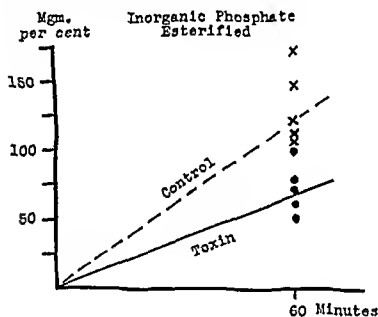


Fig 3

administration of toxin. It is evident that the amount of toxin used and the time intervals resulted in a marked loss of glycogen *in vivo*, regardless of the control level.

The loss of liver glycogen *in vivo* could have been due to an increased rate of glycogenolysis, a decreased rate of glycogenesis, or both. That increased glycogenolysis was an important factor was shown by the results of the experiments *in vitro* which are summarized in figure 2. Finely minced liver was suspended in Hasting's Ringer Phosphate and incubated at 38° C. The samples of normal liver exhibited rates of glyco-

initial glycogen level at all values of the latter. Thus at initial liver glycogen levels of 50 to 60 per cent,<sup>4</sup> the rate of glycogenolysis was more than twice as rapid in the samples of toxic liver as in those of the normal.

An indication of the pathway through which the excessive glycogenolysis induced by toxin occurred was gained by observing the disappearance of inorganic phosphate when the minced liver was incubated in phosphate buffer (M/15) at pH 7.4. Sodium fluoride (0.2 per cent) was added to inhibit dephosphorylation (20). Figure 3 shows that the rate of phosphorylation in toxic liver was only about half that in normal liver. It was evident that the more rapid breakdown of glycogen caused by toxin must proceed by a pathway other than phosphorylation. However, since the formation of glycogen is also by phosphorylation, the diminution of this process might partly account for low initial liver glycogen values in toxic liver on the basis of interference with glycogenesis.

<sup>4</sup> In order to be able to compare normal and toxic liver samples at equivalent glycogen levels in this range, it was necessary to add glycogen to some of the minced preparations of the latter samples. The finding that the rate of glycogenolysis depended partly upon the initial glycogen level made it essential to obtain other data in relation to initial glycogen levels. Additions of glycogen to liver mince were therefore made whenever necessary for comparative purposes.

<sup>3</sup> The phosphate attached to hexoses was calculated according to the formula

$$P_{100} = \text{phosphate appearing after 100 min hydrolysis}$$

$$P_7 = \text{phosphate appearing after 7 min hydrolysis (mainly adenosine triphosphate)}$$



If the abnormal pathway for increased glycogenolysis were due to amylase activity, one would expect it to occur in the absence of phosphate in the medium, providing sufficient chloride ions were present for its activation. Figure 4 shows that this prediction was fulfilled. When incubated in a medium of 0.85 per cent NaCl, specimens of minced toxic liver still exhibited an excessive rate of glycogenolysis as compared to normal liver. The unavoidable presence of about 6 mg. per cent of phosphate derived from the

despite a diminished phosphorylosis. This indicates a limitation of the normal mechanism for hepatic glycogenesis and glycogenolysis with the appearance of an abnormal pathway for glycogenolysis. The facts that the excessive glycogenolysis in toxic liver was also demonstrated in a phosphate-poor medium, and that it gave rise to characteristic endproducts not found in normal liver, point to amylase activity as the abnormal process unleashed by the toxin.

Insulin exerts a regulatory influence, direct or in-

TABLE 2. OCCURRENCE OF POLYSACCHARIDES IN LIVER DAMAGE

| No.             | Before Toxin |           |            |                |               | After Toxin |           |            |                |               |
|-----------------|--------------|-----------|------------|----------------|---------------|-------------|-----------|------------|----------------|---------------|
|                 | Total CHO    | Glyco-gen | Free sugar | Hexose-phosph. | Poly-sacchar. | Total CHO   | Glyco-gen | Free sugar | Hexose-phosph. | Poly-sacchar. |
| 19              | 2433         | 2155      | 247        | 33.3           | ±0            | 1758        | 1185      | 312        | 39.9           | 221           |
| 20              | 5486         | 5142      | 392        | 53.6           | ±0            | 3614        | 2634      | 293        | 63.6           | 629           |
| 21              | 5624         | 5252      | 302        | 60.5           | ±0            | 1724        | 1284      | 256        | 62.9           | 122           |
| 22              | 3554         | 3308      | 170        | 73.8           | ±0            | 1320        | 895       | 200        | 84.9           | 140           |
| 23 <sup>1</sup> | 1002         | 610       | 123        | 49.4           | 220           | 321         | 71        | 53         | 47.0           | 150           |
| 24              | 6585         | 6457      | 129        | 37.6           | ±0            | 2337        | 1853      | 245        | 33.6           | 186           |
| 25              | 3712         | 3396      | 344        | 54.3           | ±0            | 970         | 369       | 158        | 74.9           | 368           |
| 26              | 3784         | 3530      | 143        | 48.7           | 62            | 1575        | 1070      | 193        | 55.7           | 256           |

<sup>1</sup> Marked distemper, fatty liver. All values in mg. %

liver itself was sufficient to account for the slow rate of glycogenolysis observed in the normal liver under these conditions.

Finally, the abnormal activity of amylase in toxic liver was confirmed by the demonstration of the presence of one of its characteristic endproducts, which is not found in normal liver. Table 2 summarizes the data on carbohydrate partitions made on liver samples removed before and after toxin administration, and immediately frozen in carbon dioxide ice to prevent any autolytic change. With two exceptions, the control liver samples contained no other carbohydrate than glycogen, free sugar and hexose phosphates. In tissue from dog 26, the amount of other carbohydrate was hardly significant. Dog 23 was interesting in that its liver, which did contain a significant amount of other carbohydrate, was obviously not normal. After toxin administration, all of the specimens of liver contained significant amounts of the abnormal carbohydrate. This moiety was not precipitable by alcohol, yielded free sugar on acid hydrolysis, and was probably a mixture of dextrans.

#### SUMMARY AND DISCUSSION

Carbohydrate partitions and determinations *in vitro* of enzyme activity were made on samples of liver removed from nembutalized dogs before and after the administration of suitable amounts of diphtheria toxin. The samples obtained after toxin administration revealed an increased rate of glycogenolysis

direct, on the normal mechanism of glycogenolysis by phosphorylosis. It is not known to influence amylase activity. Hence the relative impotence of insulin (insulin resistance) in toxemic states, in which amylase activity has become a factor in hepatic glycogenolysis. This situation is probably aggravated by the interference with phosphorylosis by the toxin. That proportion of the glycogenolysis which is still proceeding by phosphorylosis may not be as responsive as it normally is to hormonal control. Also, glycogen synthesis is undoubtedly interfered with (21). Thus it is not difficult to account for the characteristically low level of liver glycogen, the 'diabetic type' of dextrose tolerance curve and the occasional hyperglycemia and glycosuria found in the initial stages of toxic liver damage. In cases of advanced liver damage, when interference with glycogen synthesis and with blood sugar formation has become extreme, hypoglycemia may result (6). In diabetes mellitus complicated by toxemia the above effects are first seen as an increased requirement for insulin, or as a lack of control by even extremely large doses. But severe liver damage may cause an apparent improvement in the diabetes, as the general clinical condition of the patient deteriorates (22).

These results also supplement the rationale for high carbohydrate therapy in liver disease (23) and for high carbohydrate therapy plus insulin in diabetes complicated by liver damage (24). It has been demonstrated previously that the addition of dextrose to

normal minced liver *in vitro* reduces the rate of appearance of free sugar from the liver itself (25) and previously administered insulin reinforces the anti glycogenolytic effect of a given amount of added dextrose (26). The present results may indicate that in the liver damaged by toxin the therapeutically increased supply of blood sugar also helps to push the glycogen glucose equilibrium in the direction of glycogen by simple mass action on the amyolytic enzymes

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# Arteriosclerosis and Hypothyroidism: Observations on Their Possible Interrelationship

## [Thyroid and Arteriosclerosis]

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IT IS WELL recognized that after the age of 40 years the basal heat production tends to decrease (1, 2, 3). DuBois (4) studied the metabolism of an individual from the age of 31 to 54 years and presented excellent evidence of a decline in the basal metabolic rate with advancing age. Generally, the decrease in metabolism has been ascribed to involutionary changes which take place in the thyroid gland; undoubtedly, other factors play a part but these will be discussed later. It appears plausible that the advent of arteriosclerosis may be correlated at times with decreased activity of the thyroid gland. At least, some observations have been carried out on animals which would lend support to such a hypothesis.

In 1913, Anitschkow (5) and Wacker and Hueck (6) demonstrated that the aorta of rabbits fed diets high in cholesterol frequently became atherosclerotic. Since then, this observation has often been confirmed and the degree of atherosclerosis thus produced in general was found to parallel the elevation in blood cholesterol. Moreover, there appears to be some relationship between hypercholesterolemia and this atherosclerotic lesion in man since atherosclerosis is not uncommon in such diseases as diabetes, nephrosis, myxedema, lipoid granulomatosis and hypercholesterolemic xanthomatosis. When rabbits were fed potassium iodide, thyroxin or thyroid substance simultaneously with cholesterol, atherosclerosis of the aorta was inhibited (7-13). This observation indicates that in the experimental animal at least, some antagonism exists between the thyroid gland and the susceptibility of the vascular tree to lipid infiltration.

In the present study, the possible relationship between arteriosclerosis and the activity of the thyroid gland was applied to the human problem. Investigations were carried out on subjects 55 years or older

and in each instance, the basal metabolic rate was correlated with the presence or absence of arteriosclerosis according to the clinical criteria described below.

### MATERIAL AND METHODS

The records of 24,000 basal metabolic rate determinations<sup>2</sup> were reviewed. The studies were made on both ambulatory and hospitalized patients at the Respiration Laboratory of the New York Post-Graduate Hospital from Jan. 1, 1930, to July 1, 1940.

The gasometer method as modified by Bailey (14) was the method used. Carbon dioxide and oxygen were determined in expired air by the Haldane (15) method as modified by Henderson (16) and Bailey (14). Each step was checked from the calculation sheets outlined by Boothby and Sandiford (17). The basal metabolic rate was compared with Aub-DuBois Standard as modified by Bailey (18). These standards are almost identical with those published by Berkson and Boothby in 1936 (19) and give most accurate results for all types of cases (20-23). For the actual procedure, most of the accepted methods were followed. The subject was tested before breakfast after a 12 to 15-hour fast. The various factors influencing the basal metabolic rate such as age, sex, height, weight, pulse, temperature and respiratory rate were recorded. The patient was put at rest on a comfortable cot located in a room furnished to resemble any home sittingroom. The gasometers and the apparatus used for gas analyses were kept in an adjoining room so as not to overwhelm the patient. With the patient at rest, his confidence and cooperation were quietly secured. The mask was a French type, used in conjunction with a rubber flutter valve introduced by the British in the first World War, as adopted by Bailey (14, 24). It was firmly applied over

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<sup>2</sup> With permission of Dr. Cameron V. Bailey.

the entire face of the subject. This type of mask caused no discomfort or increased respiratory rate such as might be induced by a mouth-piece and nose-clip to sensitive patients. These modifications helped to allay fear and allowed for complete body rest.

From the 24,000 records obtained by the above method, 755 were of patients 55 years or older. However, only 293 records were accepted for analysis. The remainder were discarded because of incomplete data, cardiac decompensation, thyroid disorders, blood dyscrasias, history of previous thyroidectomy or treatment with iodides, thyroid extract or roentgen ray. The present study, therefore, was confined to 293 subjects who were 55 years or older, and in whom no metabolic disorders or other factors were present which might abnormally influence the basal metabolic rate.

The clinical records of the subjects thus chosen were then reviewed with a view to determining the presence or absence of arteriosclerosis. The clinical criteria used were a), peripheral vascular thickening, tortuosity, beading or absent pulsation, b), intermittent claudication, c), vascular changes in the ocular fundi, d), roentgen ray evidence of peripheral arteriosclerosis and of widening or thickening of the aorta

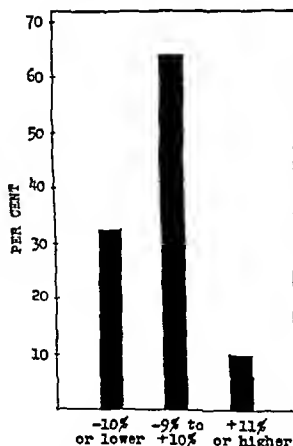


FIG 1 FREQUENCY DISTRIBUTION OF BASAL METABOLISM IN 293 SUBJECTS OVER THE AGE OF 55 YEARS

or its arch; e) wide pulse pressure, and f) urine an analysis indicative of nephrosclerosis.

No attempt was made to grade the degree of arteriosclerosis. If any subject satisfied at least two of the criteria outlined above, arteriosclerosis was considered to be present and, as will be seen later, this

crude procedure proved, nevertheless, to be fairly accurate.

#### RESULTS

Figure 1 indicates the frequency distribution of the basal metabolic rate for the total group of 293 patients. Of these, 27 per cent had a B.M.R. of 10 per cent or more below the average normal, 64 per cent

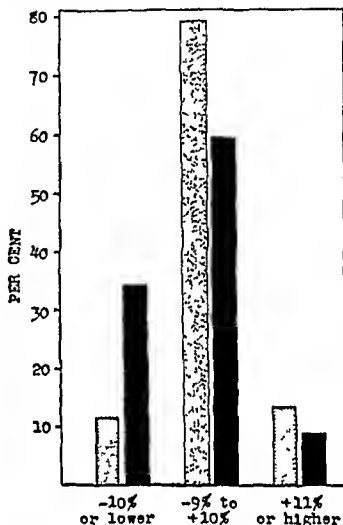


FIG 2 FREQUENCY DISTRIBUTION OF BASAL METABOLISM IN 223 SUBJECTS WITH ARTERIOSCLEROSIS (SOLID RECTANGLES) AND IN 70 SUBJECTS WITHOUT ARTERIOSCLEROSIS (SHADED RECTANGLES) OVER THE AGE OF 55 YEARS

were between 10 per cent below and 10 per cent above the average normal, and 9 per cent were 11 per cent or more above the average normal. There is, therefore, a tendency for the basal metabolic rates of patients over the age of 55 years to shift to the low side of normal as compared with observations made by Boothby and Sandiford for all age groups (2, 21). The latter workers found that 92 per cent of normal individuals have a basal metabolic rate within 10 per cent below and 10 per cent above the average normal.

Figure 2 shows that the incidence of hypometabolism (10% or more below the average normal) in non-arteriosclerotic subjects is only 10 per cent as compared with an incidence of 32 per cent in persons with arteriosclerosis. Furthermore, the distribution of basal metabolism values in non-arteriosclerotic subjects is quite similar to what may be expected in the average population, namely, 77 per cent exhibiting a basal metabolism between 10 per cent below and 10 per cent above the average normal and the re-

mainder equally distributed at the extremes. It may be stated, therefore, that the general metabolic trend downward in persons 55 years and older may be ascribed to the greater incidence of a lowered basal metabolic rate in those manifesting arteriosclerosis.

In figure 3, the individual basal metabolic rates of the 293 subjects are plotted against age. Since 76 per cent of the individuals studied showed some evidence of arteriosclerosis, two disproportionate groups are segregated, namely, 223 subjects with arteriosclerosis and 70 without arteriosclerosis. This figure demonstrates that between the ages of 55 and 65 years, the average basal metabolic rate for both groups tends to rise slowly and then declines after the age of 65 years. A pronounced decrease in the average basal metabolic rate occurs in arteriosclerotic patients 70 years or over, but comparable figures could not be obtained in the non-arteriosclerotic subjects since no person in this age group could be classed as free from arteriosclerosis by the criteria already outlined.

#### DISCUSSION

As mentioned before, it appears justifiable to assume that a hypofunctioning thyroid gland may be a factor in aiding the deposition of cholesterol in the vascular tree. Leary (25), too, intimates that decreased thyroid activity may hasten the atherosclerotic process. It should not be overlooked, however, that arterial disease may be primary and that atherosclerosis of the arteries supplying the thyroid gland may result in a diminution in the functional capacity of the thyroid gland. There is, perhaps, somewhat more evidence in support of the first assumption although, of necessity, most of it is derived from experiments on animals.

Much controversy has existed over the rôle cholesterol plays in the pathogenesis of arteriosclerosis.<sup>1</sup> Leary (25), particularly, has maintained that hypercholesterolemia will hasten the arteriosclerotic process in human beings, and has championed the thesis that the experimental atherosclerotic plaque commonly seen in the aorta of cholesterol-fed rabbits is the counterpart of the lesion seen in human tissue. Grotel et al. (26) concluded, after a study of human pathologic material, that a definite relationship existed between excessive intake of cholesterol and the development of arteriosclerosis. Davis, Stern and Lesnick (27) reported higher cholesterol levels in the blood of patients with angina pectoris of arteriosclerotic origin than in normal subjects. Poindexter and Bruger (28) presented evidence of a significant increase in the plasma cholesterol in patients with hypertensive and arteriosclerotic heart disease. On the other hand, Duff (29) argued that the atherosclerotic lesion produced in rabbits by the feeding of cho-

lesterol is not identical with that of human arteriosclerosis. Weiss and Minot (30) and Watson and Wharton (31) stated that a high cholesterol diet alone is not the chief factor in the development of the arteriosclerosis in humans. Page, Kirk and VanSlyke (32), maintained that arteriosclerotic changes in patients with hypertension were not caused by hyper-

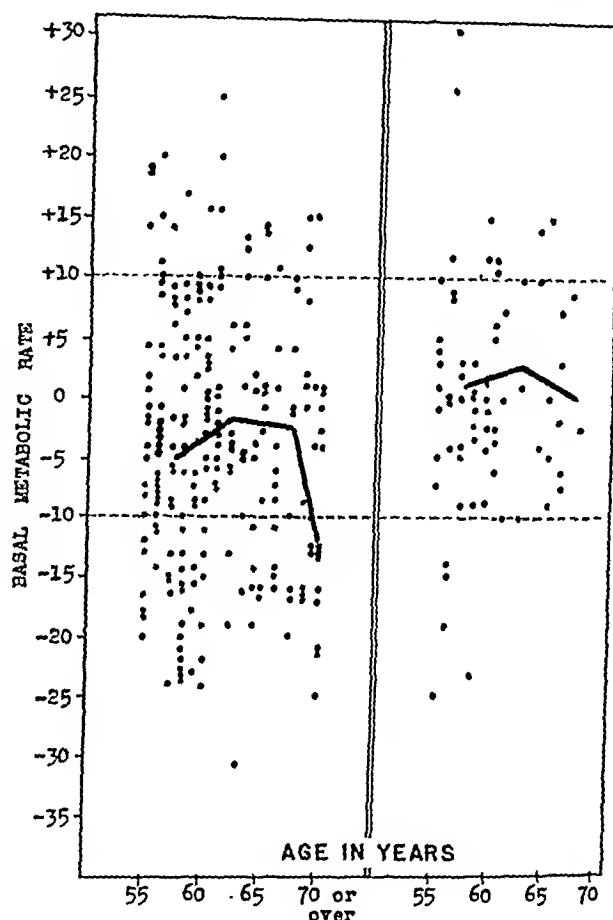


FIG. 3. CORRELATION OF INDIVIDUAL BASAL METABOLIC RATES WITH AGE IN 223 SUBJECTS WITH ARTERIOSCLEROSIS (left segment) and in 70 subjects without arteriosclerosis (right segment) over the age of 55 years. The average basal metabolic rate in 5-year periods for each group is indicated by the solid lines.

lipemia, hypercholesterolemia, or by an elevation in cholesterol:phosphatide ratio. Landé and Sperry (33) likewise maintained that there was no relationship between the degree of atherosclerosis and the level of serum cholesterol. Page (34) concluded that hyperlipemia was not essential for the development of atherosclerosis. Elliot and Nuzum (35) reported that patients with essential hypertension, with or without arteriosclerosis, did not have an elevation in blood cholesterol.

As indicated previously, the consensus of opinion has been that in diabetes, in which elevated blood cholesterols are not infrequently encountered, atherosclerosis develops more rapidly (36-42). Yet this, too, is by no means settled. Hunt has shown (43) that the

most advanced arteriosclerosis may be found in patients with comparatively low levels of plasma cholesterol Warren (44), however, believed that the feeding of diets high in fat and rich in cholesterol to diabetics in the decade between 1920 and 1930 increased the incidence of arteriosclerosis.

The basal metabolic rate was used here as an index of thyroid activity. Of course, it may be questioned whether a decrease in basal metabolic rate in older persons actually indicates a hypofunctioning thyroid gland. Lorand (45) is in favor of this view. On the other hand, it might be argued that in senescence, persons tend to ingest less food, thereby causing lowered heat production. It has been shown, however, that with diminished food intake or omission of various dietary factors, thyroid structure as well as function might be modified or impaired (46-49). Whatever the cause, dietary or otherwise, the end result is diminished thyroid activity.

It is conceivable that other endocrine glands may in some way influence the arteriosclerotic process. Yet, gonadotropic hormones (testosterone propionate and estradiol dipropionate) have not been found to inhibit atherosclerosis in rabbits as consistently as do thyroid extracts, thyroxin or iodine. Ludden, Bruger and Wright (50) have shown that these steroid hormones do not inhibit cholesterol induced atherosclerosis in male rabbits but they do exert this effect in female rabbits. Bruger and Fitz (51) have shown that the pituitary gland, more specifically the thyrotropic factor of the anterior lobe, does not prevent the deposition of cholesterol in the aorta. On the contrary, if thyrotropic factor of the anterior pituitary and cholesterol are administered simultaneously to rabbits over a relatively long period of time, there appears to be an increased deposition of cholesterol in the aorta.

Postmortem studies by Cooper (52), McCarrison (53), and by Dogliotti and Nizzi Nuti (54) demonstrated that, in older persons, the thyroid gland is reduced in size, the follicles and cells are smaller, the amount of connective tissue is increased and the colloid in the vesicles may be less dense or absent. It would appear, therefore, that the diminished function of the thyroid gland in older persons may be ascribed to these histologic changes. Carlson (55) questions this assumption since he believes there may be very large factors of safety in the thyroid gland.

Wilder (56) feels that the presence of arteriosclerosis cannot with certainty be determined by an examination of living persons. It is also conceded that in very old persons there may be no manifestations of arteriosclerosis, and again Ophuls (56) has shown that arteriosclerosis may be present in comparatively young individuals. Despite these objections, on re-

examination of our data, it is noted that even by the crude criteria outlined above, our method of classifying arteriosclerosis seems to be fairly accurate. Without age being used in the diagnostic criteria, it is found that those who were classed as non arteriosclerotic were not older than 68 years of age. This is what may be expected, since by far the largest number of subjects manifesting arteriosclerotic changes were over the age of 68.

We are in agreement with those who feel that no single factor explains the etiology of arteriosclerosis in human beings, on the contrary, the problem of its pathogenesis is a complex one. The observations referred to earlier in this paper showed the influence the thyroid gland exerts on the production of experimental atherosclerosis, although it should not be implied that only those substances affecting the activity of the thyroid gland modify the degree of atherosclerosis experimentally induced by feeding cholesterol. Malisoff (57), Strauss (58), Thiersch (59), Eberhard (60) and Huber et al. (61) have shown that the administration of potassium thiocyanate, colloidal silicic acid, garlic oil, alcohol and lipocaine, respectively, may inhibit experimental atherosclerosis. Page (34) is led to the concept that a tissue (vascular) susceptibility factor to the imbibition of lipids must exist in order to explain the fact that whereas atherosclerosis of the aorta may be inhibited by feeding iodine to cholesterol fed rabbits, the degree of hypercholesterolemia remains unaffected. It is conceivable, though of course far from proven, that the receptivity of the vascular tree to the deposition of lipids may vary inversely with the activity of the thyroid gland.

#### CONCLUSIONS

The incidence of hypometabolism in subjects 55 years or older is greater for those exhibiting arteriosclerosis than for those without arteriosclerotic manifestations. Some theoretical considerations correlating the activity of the thyroid gland and the aging process are discussed.

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# Effect of Male Hormone Therapy on Urinary Gonadotropins in Man<sup>1</sup>

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A NUMBER OF INVESTIGATORS have reported on the urinary excretion of gonadotropins following treatment of women with the steroid sex hormones. With the use of either estrogens (1-4) or androgens (3, 5, 6, 7) the increased gonadotropic output of ovariectomized or menopausal women can be abolished, although with small doses of estrogens there may be no material reduction in the titers (8).

Few studies relate to gonadotropin excretion in castrate males treated with the male sex hormones. Frank and Salmon (9) using rather limited doses of androsterone, dihydroandrosterone benzoate, and testosterone reported only slight amelioration of castration symptoms, and no influence on the excretion of gonadotropins. In a preliminary note (10) the present authors reported a definite decrease in the elimination of gonadotropins following administration of testosterone propionate to castrate males. These results are included in this paper.

## METHODS AND SUBJECTS

Urine specimens for 24 consecutive hours were collected, preserved under refrigeration with 3 cc of toluene per liter, and shipped within 24 hours to the laboratory. Gonadotropic hormone was extracted by the method of Freed and Hechter (11). Bioassays were performed using 21 to 23 day old mice from our own stock. They were injected in groups of 3 to 5 animals at dosage levels that were inferred roughly from previous trials. The animals received 6 injections spaced over 36 to 40 hours and were killed at 72 hours. We have employed, with some modification, the technique of Levin and Tyndale (12) which utilizes the uterine weight response as the criterion of gonad-

otropic activity. We define a mouse unit as that amount of hormone which under standardized conditions causes an increase of 100 per cent in the ratio of uterine weight/body weight. All unitages are expressed in mouse units (M U) per 24 hours. The response to 0.1 international unit of equine gonado-

TABLE 1. CLINICAL AND ENDOCRINE DATA ON GROUP OF SUBJECTS STUDIED

| Case No and Status  | Age | Ht    | Wt   | Urinary excretion prior to treatment or after cessation of therapy for several weeks |           |           |
|---|-----|-------|------|--|-----------|-----------|
|   |     |       |      | Gonadotropins  | Androgens | Estrogens |
| 11. Castrate for 20 yr  | 43  | 172.5 | 66.8 | M U 30-140   | 1 U 8     | 1 U 28    |
| 12. Castrate for 26 yr  | 45  | 156   | 69.0 | 50-70  | 3         | 11        |
| 13. Castrate for 13 yr  | 56  | 180   | 72.0 | 30-80  | 9         | 5         |
| 14. Castrate for 13 yr  | 39  | 162.5 | 73.6 | 10-40  | 11        | 15        |
| 15. Castration phenomena since attempted repair of bilateral hernia 2 yr before   | 43  | 170   | 81.8 | 30   | 23        | 25<br>35  |
| 16. Unilateral cryptorchid till 35th yr when descended testis was removed surgically with immediate severe and sustained castration phenomena | 35  | 177   | 70.5 | 40-240   | 13.5      | 8         |

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tropin approximates one such m.u. (Catchpole, unpublished data).

The present study concerns 4 castrate male subjects and 2 men who developed primary gonadal insufficiency following attempted repair of indirect inguinal hernias (table 1). Three of these men were studied over a period of more than two years. The plan of the experiment involved successive periods

number and nature of hot flushes, sweating and penile erections.

# RESULTS

Table 1 summarizes the clinical data together with those of the gonadotropic and sex hormone assays performed either prior to the present course of treatment, or during periods of nontreatment. The data on sex hormone output were obtained in collabora-

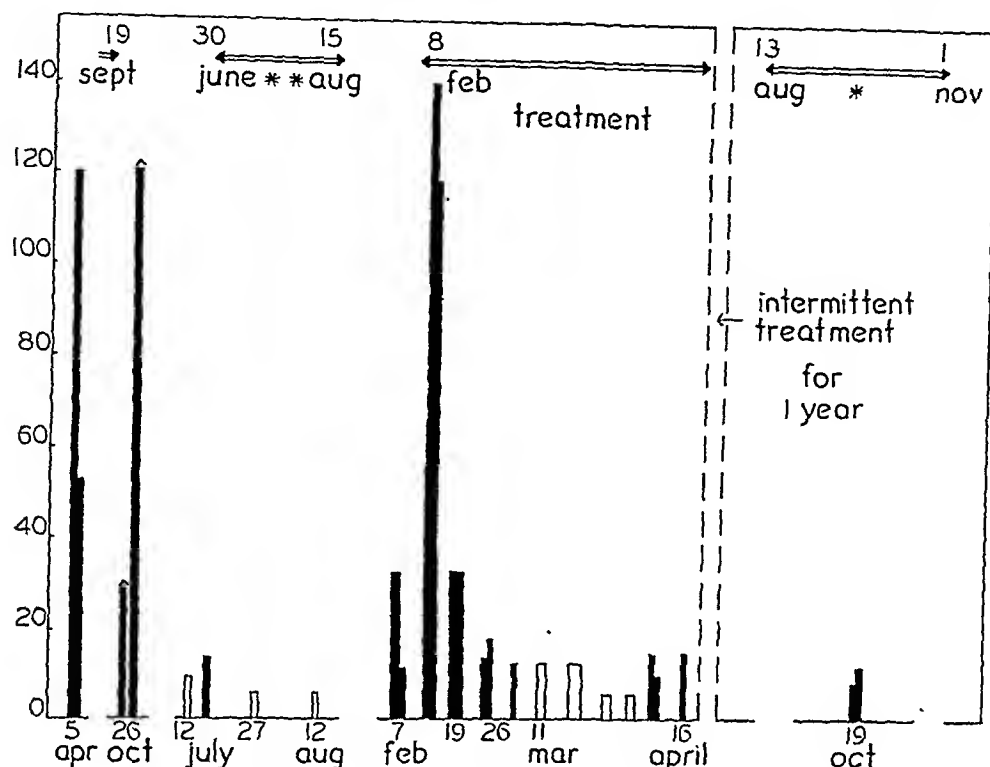


Fig. 1. EXCRETION OF GONADOTROPIC HORMONE in case 11 during periods of nontreatment, and treatment with androgens. The androgens used were testosterone propionate given intramuscularly, pellets of testosterone propionate implanted subcutaneously (\*\*), and methyl testosterone given orally (\*).

In figures 1 to 4, clear columns indicate that assays for gonadotropin were negative at the level tested. The sign  $\wedge$  indicates amounts greater than tested levels.

in which therapy with androgenic hormones was alternately given and withheld.

Several methods of administration of the hormones were tried. Testosterone propionate<sup>2</sup> was injected intramuscularly in peanut oil solution or implanted subcutaneously in the form of pellets. Tablets of methyl testosterone<sup>2</sup> were given by mouth. Gonadotropic assays were made on the urines of these patients at frequent intervals before, during and after courses of hormone administration. In order to guard against failure to detect small amounts of hormone occurring either normally or as a result of medication we have always attempted to obtain 2 or more urine specimens on consecutive days. The patients kept daily records of certain subjective changes such as the

tion with Dr. R. I. Dorfman, and are reported elsewhere (13). Values for the urinary hormone excretions are given for subjects 13 and 15 to supplement the scanty data available for such in castrate men; these individuals were not studied with respect to gonadotropic excretion following androgenic therapy.

Considerable variation was found in the daily excretion of gonadotropic hormone not only between different subjects but also in the same subject.

# CASE REPORTS

**Case 11 (fig. 1).** Preliminary assays showed an excretion of 50 to 120 m.u. of gonadotropins in April, 1938. Daily intramuscular injections of 20 mg. of testosterone propionate in oil were given from July 11th to Sept. 19th. By Oct. 26th all effects of this treatment had subsided, two determinations showing greater than 30 m.u., and 120 m.u. of gonadotropins respectively. This indicated that the titer had not changed appreciably from that observed prior

<sup>2</sup> Testosterone propionate (Perandren) and methyl testosterone (Metandren) were supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

to medication. On June 30th of the following year an amount of 280 mg of testosterone propionate was implanted subcutaneously as pellets. By July 12th tests showed that urinary gonadotropins had diminished to an equivocally positive value of 10 m u. On July 17th the assay values were 14 m u and subsequent tests during the months of July and August were negative. After extrusion of many of the pellets in the middle of August the patient did not again receive therapy until Nov 21st when 20 mg of testosterone propionate daily was given intramuscularly in oil until Dec 27th of that year. After more than a month without treatment, daily injections of 20 mg of testosterone propionate were resumed on Feb 8, 1940. Two preliminary assays showed 25 and 10 m u of gonadotropins on successive days. The reason for these low values is unexplained, since assays performed 5 and 6 days after initiation of treatment showed 120 and 140 m u respectively. With continued androgenic treatment

70 mg per day on August 20th for effective clinical control. Two months later, assays performed on October 19th and 20th were positive for 6 and 12 m u of gonadotropin per 24 hours respectively, showing that pituitary suppression had been obtained.

**Case 12 (fig 2)** Initial titers of 65 to 70 m u of gonadotropins were found in the urine of this subject in September, 1938. Treatment with 20 mg of testosterone propionate in oil intramuscularly 2 times weekly beginning

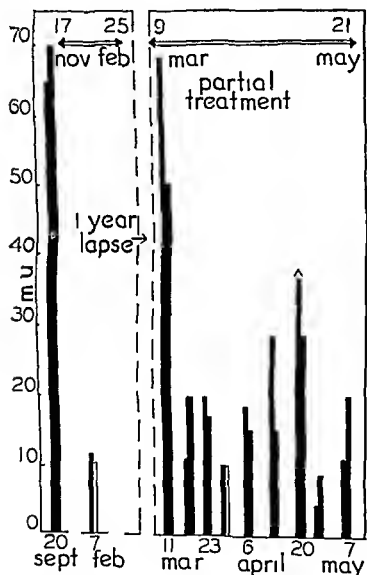


Fig 2 EXCRETION OF GONADOTROPIC HORMONE IN CASE 12 during periods of non treatment and treatment with testosterone propionate intramuscularly

the patient excreted diminished quantities of gonadotropins and after March 11th the findings were usually negative for tests of 6 to 10 m u. It was interesting to note that during the course of treatment small 'escape' amounts of gonadotropic hormone were occasionally found. After the lapse of a year during which treatment was given intermittently, a further course of therapy was begun on Aug 13, 1941. The subject received 35 mg of methyl testosterone daily by mouth, this dose being increased to

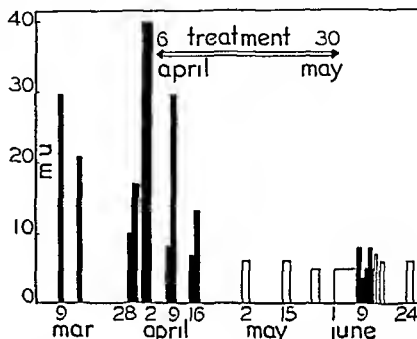


Fig 3 EXCRETION OF GONADOTROPIC HORMONE IN CASE 14 during periods of non treatment and treatment with testosterone propionate intramuscularly

in November and carried through Feb 25, 1939, produced a diminution of the urinary gonadotropins to around 10 m u. In March, 1940, after 1 year without treatment, preliminary assays showed that the titers had increased to 52 and 70 m u. The patient then received treatment with 20 mg of testosterone propionate in oil 5 or 6 times per week, during which time there seemed to be a definite reduction in the urinary values to a mean of 17 m u with a range of 5 to > 40 m u. Thus the treatment was apparently inadequate to secure complete suppression of pituitary gonadotropin output, and it is noteworthy also that this dosage was only partially successful in abolishing the clinical symptoms of castration.

**Case 14 (fig 3)** Initial assays prior to treatment of this patient showed gonadotropin values ranged from 10 to 40 m u. Following inception of treatment with 20 mg of testosterone propionate intramuscularly 5 to 6 times weekly, gonadotropic activity had disappeared from the urine before the end of the fourth week of treatment. Eight days after cessation of injections the urine titer remained negative, with small amounts reappearing in constantly in the course of the next two weeks. It was somewhat unfortunate that this patient was selected for numerous determinations, since the relatively low castrate values precluded the more extensive changes usually observed upon administration of hormone and upon withdrawal of treatment.

**Case 16 (fig 4)** Preliminary assays in January, 1938, showed titers of urinary gonadotropins ranging from 80

to 240 M.U. Thereafter, during the intramuscular administration of 20 mg. of testosterone propionate daily, high values were recorded for at least the next 10 days; subsequently lower values of 40 to 18 M.U. were encountered. Ten days after cessation of treatment, titers of 60 M.U. were recorded. High values continued unabated during a period of oral treatment with 60 to 120 mg. of methyl testosterone daily. For example, at the end of this period (April 22nd) titers of 140 and 160 M.U. were observed. Within 2 weeks after the beginning of daily intramuscular injections of 20 mg. of testosterone propionate, values for urinary gonadotropins were reduced to less than 20 M.U.

not well known. Hamburger (15) injected whole urine in mice and employed vaginal smears and ovarian histology as criteria of gonadotropic activity. He found in a series of 14 castrate subjects that 10 excreted between 100 and 500 M.U. per liter, 3 had undetectable amounts and 1 showed between 0 and 300 M.U. per liter. His technique would not appear to permit recognition of quantities of hormone much less than 100 M.U. per liter.

All six men described in the present report as well as four other men castrated prepubertally<sup>3</sup> have ex-

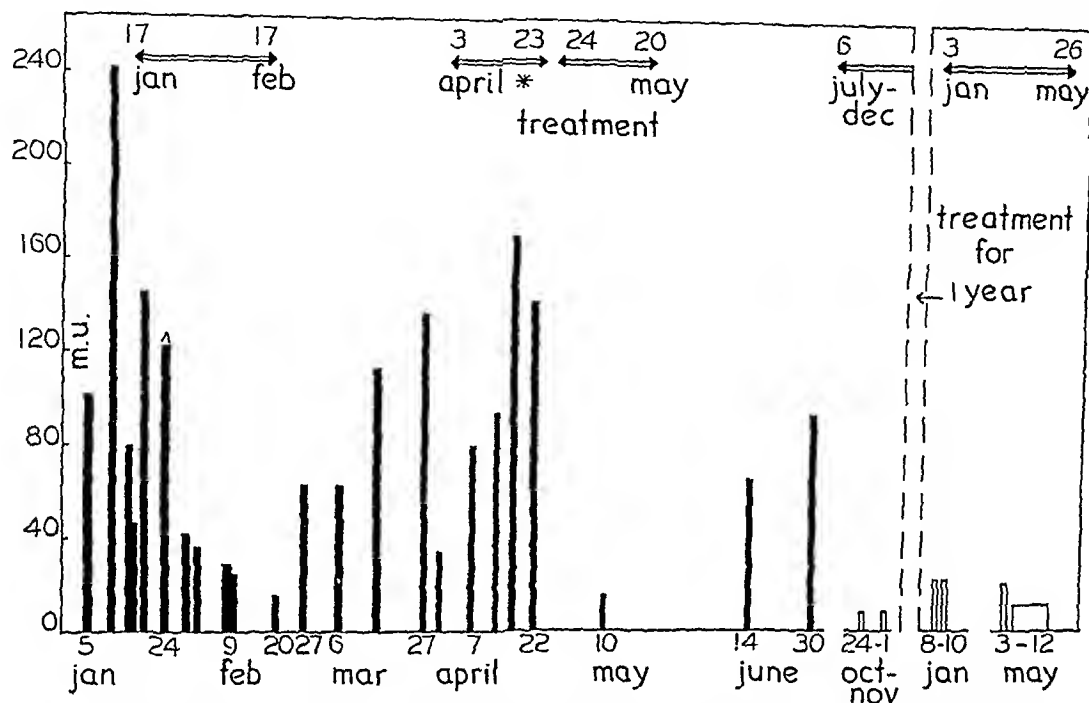


Fig. 4. EXCRETION OF GONADOTROPIC HORMONE in case 16 during periods of nontreatment and treatment with testosterone propionate intramuscularly, and with methyl testosterone given orally (\*).

twenty-five days after the last injection, values of 75 to 95 M.U. were recorded. From July 6th to September 11th the patient was placed upon a daily maintenance dose of 20 mg. of testosterone propionate, intramuscularly. As this quantity failed to provide satisfactory clinical control, the dosage was increased to 40 mg. on September 12th and assays in late October and early November, 1938, showed urinary gonadotropin titers of less than 10 M.U. Thereafter a dosage of 30 mg. was found to be satisfactory, and this was continued for a period of one year. On Dec. 20, 1939, treatment was discontinued for 13 days, and was begun again on Jan. 3, 1940. On January 8th and 10th the urinary gonadotropic hormone titer was still negative, and during 9 consecutive days in May of the same year consistently negative values (less than 6 M.U.) were recorded.

#### DISCUSSION

Since the work of Hamburger (14, 15) it has been known that castrate men may have supranormal titers of urinary gonadotropins, but as quantitative measurements are few the typical quantities and range are

creted quantities of gonadotropins generally greater than those observed in normal men. Our data show that there exists great variability from individual to individual, and from day to day in a single person. Thus case 14 excreted quantities varying from 10 to 40 M.U., case 11 from 30 to 140 M.U., and case 16 from 40 to 240 M.U. We have found the daily excretion in normal males to be between 7 and 20 M.U. The state of general health may affect gonadotropic titers as it does the excretion of steroid substances (16, 17), but the great degree of variation during periods when the men were not ill suggests that other factors are operative in the production of deviations that exceed in some instances any probable inaccuracy due to technical procedures.

The therapeutic use of androgens in men with primary testicular insufficiency (cf. (18) for review) brings about a diminished excretion of urinary gonad-

<sup>3</sup> Hamilton and Catchpole, unpublished data.

otropins Since in animals the gonadotropic content of the pituitary is increased in castrates (19, 20) and decreased under the influence of androgens (21), it seems reasonable to suppose that alterations in urinary gonadotropins of castrate men under similar circumstances reflect changes in pituitary function. Androgenic therapy can cause lowering of the urinary gonadotropic titer from the supernormal castrate level to within the normal range, or even to amounts too small to be detected (less than 6 m.u. in this series). Continued reduction of gonadotropin titers to approximately the normal range was accomplished in case 12 by approximately 100 mg of testosterone propionate per week, given intramuscularly as 5 divided doses. Cases 14 and 11, receiving larger doses of 120 to 140 mg of testosterone propionate weekly in 6 or 7 divided doses, gave evidence of further inhibition of pituitary secretion, the urinary gonadotropin titers being reduced below normal levels. A condition of equilibrium obtains between circulating steroid hormones and the secretion of gonadotropins which is well shown in occasional escape values for gonadotropins (case 11), and in the incomplete suppression of gonadotropin excretion that occurs during minimal or subminimal therapy (case 12). The daily dosage of androgen required to suppress the hyperexcretion of gonadotropins in the castrate lies between 30 mg and something less than 20 mg of testosterone propionate, when administered intramuscularly in 1 cc of peanut oil. Individual requirements vary considerably. On the basis of clinical benefit, case 16 was found to respond best to 30 mg of testosterone propionate daily, whereas management of all other cases was achieved with 20 mg daily. This latter dose is smaller than the quantity (25 mg daily) ordinarily advocated for the treatment of castrates (22). Use of this amount in castrate men was accompanied by an increase in body weight, muscular growth and cardiovascular changes, and increased stamina, endurance and erectile ability. Further work is necessary to determine whether sexually immature men, who have reached the third decade or more, require for induction of sexual development a larger dose of androgen than that needed to maintain in postpubertal castrates a previously established stage of development.

Implantation of testosterone propionate subcutaneously in the form of pellets has been advocated as an economical procedure (23). In case 11 280 mg of testosterone propionate in the form of cylindrical pellets with a total surface area of approximately 800 sq mm was implanted on June 30, 1938. Satisfactory clinical relief was obtained and urinary gonadotropin titers were reduced to normal or subnormal values (fig. 1). Details concerning the type of pellets and the

excretion of urinary androgens are given elsewhere (24).

A limited series of observations were made when methyl testosterone was given orally. Case 16 continued to have elevated urinary titers of gonadotropic hormone during a 20 day course of treatment with

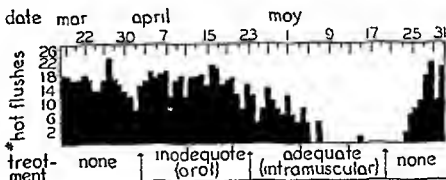


FIG. 5. CHART OF THE NUMBER OF HOT FLUSHES recorded in case 16 during periods of nontreatment treatment with methyl testosterone orally and with testosterone propionate given intramuscularly.

from 70 to 100 mg daily of this substance, no relief of symptoms occurred. However, as already noted the therapeutic requirement of injected testosterone propionate for this patient was higher than in others of our series. Greater success was obtained in case 11 who received 70 mg of methyl testosterone daily for 2 months. Both clinical relief and pituitary suppression were apparent.

Following the initiation of effective treatment, that is, treatment which will control clinical symptoms and eventually cause the disappearance from the urine of measurable quantities of gonadotropins, a decreased excretion of hormone was usually seen after 10 or 13 days, with more or less complete disappearance within 3 weeks. We attempted to use the smallest dosage compatible with clinical relief and it is conceivable that with more energetic treatment these time relations would be shortened. By continuing treatment at the maintenance level, inhibition of pituitary function may apparently continue indefinitely. Urine from case 16 gave negative tests for gonadotropins for 10 consecutive months, the longest period of treatment during which bioassays were made.

In every instance in which urinary gonadotropins had disappeared during courses of androgenic therapy there was a reappearance after cessation of treatment, in amounts as high as those observed prior to therapy. Such return to high levels has been noted after 3-month periods of intensive androgenic therapy, and to this degree at least therefore, the suppression of pituitary gonadotropic function is reversible.

In case 11, following incomplete disappearance of gonadotropic hormone from the urine there was a definite increase 7 days after cessation of treatment. In case 14 the gonadotropic hormone reappeared in

the urine 7 days after treatment was stopped, but a few days later the titer was again negative. The exact time relations of the recovery process are obscured by the possibility of residual amounts of hormone remaining at the injection sites.

As an approach to the problem of obtaining more objective and quantitative analysis of the effects of androgen therapy in castrate men, we have charted the number of hot flushes experienced daily by these individuals. In figure 5 the findings in case 16, covering a 2½ month period, may be compared with the corresponding period of therapy and hormone assay charted in figure 4. Hot flushes continued unabated during a course of treatment with 70 to 100 mg. of methyl testosterone daily given orally, but were promptly alleviated by intramuscular injections of testosterone propionate. The occurrence of hot flushes is thus related to androgenic treatment and this may be correlated to some extent with the control of gonadotropin excretion. However, we do not believe that body levels of gonadotropic hormone are causally related to vasomotor instability. Upon institution of androgenic therapy hot flushes may disappear before values of urinary gonadotropins are substantially altered, and upon cessation of therapy hot flushes may reappear promptly even before gonadotropic excretion values return to normal levels. A similar dissociation of gonadotropic titers and vascular changes has been reported in women (8, 25). Furthermore, we feel that a psychogenic factor is important in several of our patients with the most severe vascular disturbances; clinical benefit from androgenic therapy was often less during periods of stress.

#### SUMMARY AND CONCLUSIONS

1. Men with primary testicular insufficiency excrete amounts of urinary gonadotropins that are generally greater than those of normal men. Both individual and day to day variations are considerable, the range of values being from near normal to eight or ten-fold normal.

2. Testosterone propionate administered in therapeutic dosages reduced the excretion of urinary gonadotropins to undetectable amounts (less than 6 m.u. per 24 hours). Significant diminution in gonadotropic hormone excretion occurred within 10 to 13 days after the beginning of treatment, and with continued treatment the urine remained free of gonadotropins for as long as the study continued (10 months).

3. Following cessation of 3-month courses of androgenic therapy, gonadotropic titers rose to levels observed prior to treatment, detectable amounts being seen after 7 to 13 days. Thus no permanent impairment of this mechanism has been demonstrated.

4. There is no evidence of a direct relation between gonadotropic titers and the incidence of hot flushes or vasomotor instability in men with primary testicular insufficiency.

5. Although in one case 30 mg. of testosterone propionate was required for clinical benefit and control of excessive excretion of gonadotropins this was usually accomplished with a daily dose of 20 mg. of testosterone propionate injected intramuscularly in 1.0 cc. of peanut oil. This dose is about four-fifths of that usually recommended. Control of symptoms and gonadotropic excretion was obtained in one castrate patient with 70 mg. daily of methyl testosterone administered orally.

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# Vasomotor Reactions Persisting for Twenty Years in a Male

## Treatment with Androgens

### [Flushing and Male Hypogonadism]

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RHYTHMIC VASOMOTOR REACTIONS, analogous to those which occur in the menopause, are quite rare in the male. In the case to be reported here,<sup>1</sup> flushes associated with profuse perspiration first begun following testicular atrophy that supervened on a bilateral herniorrhaphy. The disturbances occurred approximately every half hour and the syndrome persisted for twenty years. Under adequate androgen therapy<sup>2</sup> the flushes and sweating disappeared, they recurred whenever the dosage was reduced below the maintenance level.

#### CASE REPORT

S.H., a 52 year-old unmarried white male, a former resident of Austria, bookkeeper by trade, was first seen on Aug. 18, 1940. He complained of flushes and perspiration which occurred about every half hour and were so severe that they interfered with his work and embarrassed him socially. Twenty five years previously he had received roentgen therapy under the chin and to the pubic region for a dermatitis that had resisted other therapy. Following this the hair in both regions fell out and did not grow back. He noticed no change in the size of his testicles at this time nor was there any diminution in libido or potency. Five years subsequently he was operated in Vienna for a bilateral inguinal hernia. Following the operation, according to the patient, he had a hemorrhage into the scrotum which was drained. Shortly after recovery from the herniorrhaphy he noticed that his testicles had diminished in size to about that of the tip of his index finger, and he thought that subsequently there was some loss of libido and potency. About this time he first began to have flushes which lasted about two or three minutes at a time and recurred at the intervals already indicated. For the ensuing 18½ years the syndrome, so far as he could tell, remained more or less constant, he received no therapy. Shortly

after coming to America in 1939 the flushes became more severe (though not more frequent), at the time of his first examination he felt them to be almost incapacitating. He had been treated about eight months previously for pansinusitis and atrophic rhinitis.

**Examination.** His height was 63 inches, his weight was 139½ pounds. The general contour of the body appeared feminine, with excessive deposition of fat over the hips, a protuberant abdomen, and gynecomastia. The skin was smooth, pubic and axillary hair were almost completely absent and there was an area of alopecia under the chin. There was no palpable enlargement of the thyroid. The penis and scrotum appeared normal but testicles could not be palpated, there was a long transverse scar just above the pubis. Except for the sinusitis and atrophic rhinitis already mentioned, there were no other abnormalities. The blood pressure was 140/80 mm. Hg, fasting blood sugar, 75 mg. per cent, basal metabolic rate, +10.

**Treatment.** The patient was first given testosterone ointment for percutaneous administration of 4 mg. and later 8 mg. of the steroid a day. This produced a noticeable increase in libido but had no effect on the flushes. Subsequently he received 25 mg. of testosterone propionate in oil intramuscularly twice a week together with testosterone from 4 to 8 mg. a day percutaneously for one month. There was gradual diminution in the frequency and duration of the flushes until at the end of the month he had only one or two fleeting reactions a day. He felt definitely stronger, and he noticed a considerable increase in libido and potency. He gained 7½ pounds.

The patient then received 10 mg. of methyl testosterone orally three times a day in place of the injections previously given, at the same time continuing 8 mg. of testosterone per day percutaneously. At the end of two weeks he was completely free of flushes and reported that he had spent 5 hours in a very warm and crowded room without a single reaction, formerly this environment would have been intolerable.

Because a further supply of testosterone propio-

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<sup>1</sup> I am indebted to Dr. Edwin G. Langrock for permission to investigate this case.

<sup>2</sup> The androgens used in this study, with the exception mentioned in footnote 3, were supplied through the courtesy of Dr. W. H. Stoner of the Schering Corporation, Bloomfield, New Jersey.

nate or methyl testosterone was not immediately available, for the ensuing three weeks he used only the testosterone ointment, 8 mg. of the steroid per day. At the end of this time the flushes had recurred and were appearing irregularly from every half to two or three hours.

Small pellets of methyl testosterone, prepared under a pressure of 6900 pounds per square inch, were then implanted.<sup>3</sup> Using the method described by G. R. Biskind (1) 16 pellets weighing a total of 150.7 mg. were inserted through a long No. 12 hypodermic needle by means of a stylet into the subcutaneous tissue of the outer aspect of the right thigh on Jan. 24, 1941. All other androgenic therapy was discontinued.

Unfortunately, at about this time the patient acquired influenza. Shortly after recovery from the attack he complained of a sore mouth and lips and was found to have a stomatitis with the purplish-red fissured tongue and the typical fissures at the corners of the mouth indicative of a predominant riboflavin deficiency. This was treated with large doses of brewers' yeast, a preparation of vitamin B complex derived from yeast and liver, riboflavin, nicotinic acid, fresh liver and parenteral crude liver extract. Later, when nicotinamide became available, it was substituted for the nicotinic acid, as the vasomotor reactions produced by the latter drug appeared to confuse the clinical picture; the patient spontaneously reported moderate improvement in the flushes promptly after this change was made. The oral lesions improved slowly, but were still detectable after several months of continuous treatment with large doses of the specific substances. Exacerbations occurred whenever he caught cold or was under unusual stress. The blood picture was normal.

After implantation of the pellets, for about 10 days or two weeks there were no flushes or only one

or two a day. Then they became gradually more frequent, occurring every 1½ to 3 hours. After about a month the pellets were no longer palpable although, judging from the lessened frequency of the flushes, some androgen was probably still present.

Injection of 25 mg. of testosterone propionate in oil intramuscularly twice a week again caused complete cessation of symptoms after five weeks. Again, when it became necessary to interrupt therapy the syndrome returned to its original status; within three weeks the patient was having flushes every half hour.

On June 20, 1941, four 75 mg. pellets of testosterone (total 300 mg.) were implanted through a small incision subcutaneously in the upper left gluteal region. Healing occurred rapidly and there was no local tenderness. Prompt improvement in the flushes followed (mild reactions occurred about every two or three hours) but this amount of androgen was insufficient entirely to control the symptoms. Judging from recent reports (1, 2) probably two or three times the amount implanted would be necessary. The pellets were still palpable 3½ months later, at which time the symptoms, while present, were so mild and infrequent that he ceased complaining about them. The androgen therapy caused no change in fat distribution and the gynecomastia was unaffected. While the sinusitis had improved there was no change in the atrophic rhinitis. No significant change occurred in the basal metabolic rate.

#### SUMMARY

An unusual case is reported of rhythmically recurring flushes persisting for twenty years in a male with secondary hypogonadism. The flushes disappeared under adequate androgen therapy and recurred whenever dosage was reduced below the maintenance level.

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<sup>3</sup> These were kindly supplied by Dr. Gerson R. Biskind of Mt. Zion Hospital, San Francisco, California.



# The Use of Male Sex Hormone in Endocrine Disturbances in Children

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## [Androgens and Genital Development]

MALE SEX HORMONE has rarely been used in the treatment of endocrine disturbances in children. Since the first reports on the use of male sex hormone there has been the fear and the danger of side effects. Male sex hormone definitively produces profound anatomical changes, such as the growth of the penis, scrotum, seminal vesicles and prostate, as well as the development of pubic and axillary hair and the hair on the extremities. There is a marked change in the texture of the skin and in addition there is an improvement in the general well-being and personality with the use of this hormone. Kenyon (1) reports that its use brings about a retention of nitrogen and sodium and a slight increase in the basal metabolic rate. Moore and Price (2) hypothesized that the sex hormones cause atrophy of the gonads by inhibition of the gonadotropic hormone of the pituitary. Recently Zelson and Steinitz (3) stated that the male sex hormone will produce an enlargement of the penis and scrotum and growth of pubic hair, but will also cause a shrinkage in the size of the testicle descended and undescended. Shay and his collaborators (4) state "the immature germinal epithelium can be stimulated by testosterone propionate to increased activity but not to an earlier maturation. Once a stage is reached at which maturation intrinsically becomes possible, testosterone propionate may stimulate maturation quantitatively. The treated animals' testes then carry more mature spermatozoa than those of the controls." They found that treating young rats with large doses of testosterone propionate causes less inhibition of growth and sperm maturation than small doses. They tentatively explain their findings thus: "Testosterone propionate is thought to stimulate the testes directly, at the same time exerting an inhibitory influence on the pituitary. This in turn inhibits the testes through inhibition of the gonadotropic pituitary hormone. During the first month of life the stimu-

lating effect is not counteracted by inhibition of the pituitary because gonadotropic function is not yet developed. Very large doses are necessary to make the stimulating effect dominant, or in other words the pituitary is more sensitive to testosterone than the testes." The reciprocal influence of the pituitary and gonad secretions seems to be one of the principal regulatory factors in the hormone secretion.

In our present state of knowledge it is impossible to state when the male sex hormone secretion is first established (5). It has been hypothesized that embryonic development of the Wolffian ducts is conditioned by secretion from the embryonic testis. Moore, in his microscopic studies on the human prostate, suggested a temporary flush of hormone secretion at birth (perhaps this is due to maternal hormones), a lower grade of secretion sufficient to cause slow growth of the prostate to about 10 years of age, then a rather sudden rush of more active secretion at puberty, a constant active secretion until the fifth and sixth decade and then a gradual diminution of hormone production. Nathanson and his associates (6) report that from 3 to 7 years of age, both boys and girls excrete a small and constant amount of estrogens and 17 ketosteroids in the urine with very little difference between the sexes. From 8 until 11 years there is an increased secretion of these hormones, the estrogens in the girls and the 17 ketosteroids in the boys. There is higher excretion of 17 ketosteroids in boys after 11 years of age. The follicle stimulating hormone appears in the urine of boys between 12 and 13 years of age.

It seems logical to believe in the theory of Shay that there will be only a stimulative effect on the testes in children, since the gonadotropic function of the pituitary is not yet developed and so no inhibitory activity can occur.

The results in the treatment of cryptorchidism with male sex hormone have been no better than with other endocrine products. The percentage of descent varies roughly from 10 to 80 (7). Zeithaml (8) re-



ported that in 8 patients with 10 undescended testicles treated with testosterone propionate no change was noted in the testes. These received from 17.5 to 145 mg. In none of these patients studied was there an observable effect on growth or body build. Zelson and Steinitz (3) reported on 20 children between 7½ and 13 years of age. Eleven had had previous treatment with gonadotropic hormone varying between 5100 and 40,000 u. There was complete descent in 15 per cent and partial descent in 45 per cent. One boy grew one-half inch and one grew 1 inch in four weeks. Subsequently (9) these authors reported on the treatment of cryptorchidism with combinations of anterior pituitary-like substance and testosterone, 53 per cent responded with complete descent of the testes.

Fourteen cases of endocrine disturbances which were treated with male sex hormone ointment<sup>1</sup> and oral methyl testosterone<sup>1</sup> are here reported. There were 5 patients with 5 undescended testicles, 7 with infantile genitalia, 1 case of hypogonadism and 1 of atrophy of a testicle following mumps.

#### CASE REPORTS

*Case 1. W.L.*, a 10½-year-old boy, was admitted on Dec. 4, 1940, to the Pediatric Endocrine Clinic with the complaints of undescended testicles and obesity. Physical examination revealed the right testicle undescended; the left was descended but was small and soft; the penis was small and there was a female distribution of fat. The B.M.R. was -3; roentgenograms of the sella and the epiphyses revealed normal structure. The weight was 127 lb., the height 61 inches. He was given gonadotropic hormone,<sup>2</sup> 10 u twice weekly and received a total of 210 units with no improvement. On May 3, 1941, he was given 4 mg. of testosterone propionate by inunction six times a week. On June 21, 1941 the penis had increased in size, pubic hair had become abundant, the left testicle was much larger and firmer, the right testicle was still undescended, the weight was 128 lb. and the height 63 inches.

*Case 2. J.G.*, a 7½-year-old boy was admitted on Feb. 10, 1941, to the Pediatric Endocrine Clinic. Physical examination revealed an obese child with a minute penis and a right undescended testicle. The B.M.R. was +2 and roentgenograms showed no abnormalities in the osseous centers. He was given methyl testosterone, 10 mg. once daily. On June 14, 1941, his condition was unchanged. However, his height was now 54 inches and his weight 92 lb. while on admission his height had been 52½ inches and his weight 89 lb.

*Case 3. A.F.*, a 10-year-old boy, was admitted on Feb. 17, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed an obese boy with a small penis and a right undescended testicle. His weight was 103 lb. and his

height 54½ inches. He was given testosterone propionate, 10 mg. weekly for four months. On Sept. 7, 1940, the right testicle was still undescended, the penis was larger, the pubic hair profuse. The B.M.R. was -1 and roentgenograms showed a slight delay in the epiphyseal centers of both pisiform bones. He was treated with testosterone propionate again for one month. On Nov. 23, 1940, there was no improvement. His weight was 120 lb. and height 57¾ inches. He was then given testosterone propionate by inunction. On Feb. 15, 1941, there was marked growth of the penis, pubic hair had increased, the left testicle was firmer, the right was not felt. On March 21, 1941, both testicles were descended. His weight was 121 lb. and his height 58½ inches. When last seen in September, 1941, the testicles were still descended.

*Case 4. H.B.*, an 11-year-old boy, was admitted on Nov. 28, 1939, to the Pediatric Endocrine Clinic. Physical examination revealed a left undescended testicle. His height was 60 inches and weight 94 lb. He received anterior pituitary-like hormone 500 u twice weekly for one year with no results. On Oct. 5, 1940, he was given testosterone propionate, 10 mg. weekly. His height at this time was 61 inches and weight 103 lb. He received treatment for one month with no improvement. He was then given testosterone propionate by inunction in addition. On March 22, 1941, there was no descent of the testicles noted. His height was 64 inches and his weight 108 lb. Therapy was discontinued.

*Case 5. I.P.*, a 7-year-old boy, was admitted on May 25, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed a left undescended testicle. His weight was 64 lb. and his height 49½ inches. He was given anterior pituitary-like hormone, 150 u twice weekly for three months with no improvement. On Sept. 14, 1940, he was given testosterone propionate, 10 mg. weekly. His weight was 62 lb. and his height 50½ inches. The roentgenogram showed the epiphyses were normal. On May 3, 1941, the testicle was still undescended and the patient was given testosterone propionate by inunction. His weight was 76 lb. and his height 52½ inches. On June 14, 1941, the testicle was still undescended. The weight was 74 lb. and the height 54 inches.

Of these five cases of cryptorchidism only one cryptorchid testicle descended. However, four of these boys showed an abnormal rate of growth and the other showed marked improvement of the secondary sex characteristics.

*Case 6. F.M.*, a 16-year-old boy, was admitted on April 14, 1939, to the Pediatric Endocrine Clinic. Physical examination revealed a typical eunuchoid. The breasts were large and fatty. The penis and testicles were very small. There was no body hair. The voice was high-pitched. The height was 64 inches and the weight 119 lb. The Wassermann reaction was 4+. He was given an anterior pituitary-like substance until Nov. 4, 1939, with no improvement resulting. His weight was now 127 lb. and his height 66¾ inches. He was given testosterone propionate, 10 mg. three

<sup>1</sup> The testosterone propionate (Perandren) and the methyl testosterone (Metandren) were supplied by the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

<sup>2</sup> Pregnant mare's serum.

times weekly and this was then increased to 25 mg three times weekly. By February, 1940, he had received about 375 mg of testosterone propionate. There was definite increase in the size of the penis, some pubic hair was visible and the voice was lower pitched. On July 30, 1940, his height was 69 inches and his weight 132 lb. The penis had further increased in size, pubic and axillary hair was present and there was a fine fuzz on his cheeks. The BMR was -3. On March 1, 1941, his height was 72 inches, his weight 142 lb. He had had no therapy for one month because of interstitial keratitis. The testicles were firm but small, the penis was normal, there was abundant hair in the pubic and axillary regions and he was shaving once a week. He was given oral methyl testosterone 10 mg three times a day and this was later reduced to 10 mg daily. In September, 1941, his condition was excellent.

**Case 7 G K**, a 9 year-old boy, was admitted on Dec 7, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed a right atrophic testicle which had followed an attack of mumps. The testicle was the size of a lima bean. The patient was given testosterone propionate, 10 mg twice weekly, for one month without results. He was then given the injections once weekly in addition to testosterone propionate ointment. In April, 1941, his general condition was good. The BMR was -1 and roentgenograms of the epiphyses showed them to be normal. The atrophic testicle had increased until it was the size of a small walnut. The patient was discharged. His height on admission was 60 inches and at discharge 60½ inches.

**Case 8 L S**, a 13½ year old boy, was admitted on March 2, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed small genitalia, no pubic hair and a high pitched voice. He was given testosterone propionate, 10 mg twice weekly for two months, with no change. On April 19, 1941, the genitalia were unchanged in appearance and the patient was given oral methyl testosterone, 10 mg daily. On May 24, 1941, the genitalia had increased markedly in size.

**Case 9 P S**, a 12 year old boy, was admitted on Jan 10, 1939 to the Pediatric Endocrine Clinic. Physical examination revealed bilateral undescended testicles. He received anterior pituitary like hormone three times weekly. On May 16, 1940, both testicles were descended. He was seen again March 7, 1941 and this time the genitalia were small and the testicles soft. He was given testosterone propionate, 10 mg weekly for three months with no change resulting. On June 7, 1941, he was given oral methyl testosterone, 10 mg every other day. In September, 1941, there was no change noted.

**Case 10 T B**, a 10 year old boy, was admitted on May 8, 1939, to the Pediatric Endocrine Clinic. Physical examination revealed infantile genitalia. A roentgenogram showed slight delay in the appearance of the pisiform bone. He received anterior pituitary preparations without results. After six months during which he received no treatment he was given testosterone propionate, 25 mg weekly

for three months which resulted in an increase in the size of the penis but not in the testicles. On April 19, 1941, his condition was unchanged and he was given oral methyl testosterone, 10 mg daily. His height was 59¾ inches, his weight 112 lb. By June of 1941, the testicles had increased in size. His height was 61 inches and his weight 113½ lb.

**Case 11 J D**, a 9-year old boy, was admitted on Feb 8, 1939, to the Pediatric Endocrine Clinic where he received gonadotropic hormone for undescended testicles which descended following therapy. He returned to the clinic because of very small genitalia and received anterior pituitary like hormone, 500 u twice weekly for one year, without improvement. On Dec 14, 1940, he was given testosterone propionate by injection. By June, 1941, the genitalia showed a marked increase in size and therapy was discontinued.

**Case 12 H S**, an 8 year old boy, was admitted on May 28, 1940, to the Pediatric Endocrine Clinic. Physical examination revealed small genitalia. The BMR was -1. He was given an anterior pituitary extract twice weekly for five months without improvement, and then was given anterior pituitary like hormone, 500 u twice weekly for two months, without improvement. On Feb 15, 1941, the testicles were small and soft and receded easily. He was given oral methyl testosterone, 10 mg daily. On June 28, 1941, the genitalia were normal in size, both testicles were firm and large and did not recede.

**Case 13 F C**, a 15 year old boy, entered the Clinic because of short stature and infantile genitalia. His weight was 81 lb his height 54¼ inches. Roentgenograms showed a delayed development of the osseous centers of both wrists. He received an anterior pituitary preparation for eight months without results. On Sept 21, 1940, he was given testosterone propionate, 10 mg weekly. His height at this time was 56 inches. He received the injections until Jan 4, 1941. The genitalia were still small, there was no change in the body hair and the voice was still high pitched. However, there was a marked improvement in the general condition. The boy was more cheerful, more active and brighter. A roentgenogram showed generalized hypo development of the bones of both hands. Treatment was stopped. On March 15, 1941, the boy was seen again. He was tired, nervous and irritable and the skin was very dry. He was given testosterone propionate by injection. On June 28, 1941, his general condition was good, the genitalia had increased markedly in size, the skin was moist and smooth and therapy was stopped. His height at this time was 57 inches and his weight 85 lb.

**Case 14 M T**, a 6 year old boy seen in the Pediatric Endocrine Clinic on Jan 25, 1941. Physical examination revealed obesity with infantile genitalia and alopecia areata. His weight was 94 lb and his height 52½ inches. He was given gonadotropic hormone, 10 u twice weekly. On May 5, 1941, there had been no change in his condition. His height was 53 inches and his weight 102 lb. The BMR was +7 and the roentgenogram showed no delay

in ossification. He was given testosterone propionate by inunction with no results after one month.

In our use of male sex hormone in children we have been particularly impressed with certain factors. One is the lack of any side effects which we were particularly careful to check. In no instance was there any complaint of priapism or ejaculations, diurnal or nocturnal. In only one case were there nocturnal ejaculations (Case 6), and we considered this result more therapeutic than otherwise.

Another striking factor was the ease of administration and the willingness of the patients to take this form of therapy. There has always been difficulty in getting children to return regularly for injections so that therapy by the intramuscular method had never been continuous. With the use of the ointment and tablets the children were much more cooperative and the dosage was easier to regulate.

The last factor which impressed us was the effect on the rate of growth in a number of these boys. In four there was a definite increase in the rate of growth over the normal. In none of the patients on whom roentgenograms were made was there premature closure of the epiphyses noted.

#### SUMMARY

Fourteen males, 16 years of age and younger, with

endocrine disturbances, were treated with testosterone propionate by inunction and with oral methyl testosterone and Metandren.

We have found the use of ointment and tablets by mouth more efficacious than intramuscular treatment in children.

No deleterious side effects were noted.

Seven boys with infantile genitalia were treated and 5 were so improved that they were discharged. Five cases of cryptorchidism were treated; only 1 cryptorchid testicle descended. Four of these boys showed an increased rate of growth. One atrophic testicle was increased in size. One eunuchoid patient improved remarkably on the therapy employed.

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# COMMUNICATIONS TO THE EDITORS

## Goiter, Iodine and Military Strength. II.

SINCE GOITER reduces military strength, its cause and distribution should be of interest at this time. The first communication<sup>1</sup> of the series supports the iodine deficiency theory of its origin but many physicians still consider the cause of goiter to be unknown. Few analyses of iodine in drinking water have been made, therefore the relation of iodine to geological formations is considered.

A reduction in goiter incidence in areas over petroleum and salt deposits has been noted.<sup>2</sup> The salt is usually formed by the evaporation of impounded sea water, but smaller deposits may arise from these by solution, transportation and re evaporation. Petroleum is often underlaid by brine and the frequency of its association with brine or salt might indicate its marine origin. An area of salt and petroleum is not uniform throughout, there being many gaps in the layers of both salt and petroleum, which would require close spacing of expensive drilling for complete mapping. Owing to its greater commercial value, the petroleum areas have been explored more thoroughly than the salt. The salt came from the ocean which is calculated to contain about 65 billion tons of iodine, and since this remains soluble after the water is evaporated, marine deposits are a valuable source of iodine to land organisms. Rocks contain more iodine per volume than sea water and some of the iodine released by weathering is retained in the soil. Soils are richer in iodine than the rocks from which they are formed. But this source of iodine alone is not sufficient to prevent goiter.

The Texas Panhandle (including the adjacent region) is unique in that the petroleum has proven valuable and a valuable deposit of potash has been the incentive for still more drilling. There are two potash mines 1000 and 1800 feet deep near Carlsbad, New Mexico tapping the earth beneath the deepest part of the sea that existed in the Permian period. The axis of this Permian deep extends northeast through the Texas Panhandle and western Oklahoma into Kansas. Salt is encountered about 700 feet below the surface and in some places it extends to about 11,000 feet.<sup>3,4</sup> To account for this great thickness (since ocean water is only 3.5% total solids) it is supposed that this Permian sea maintained a connection with the ocean which fed in more water as it evaporated. From the area of the deposits (about 100,000 square miles) and the ratio of iodine to salt in sea water, it may be calculated that the deposits contain about 30 million tons of iodine—on the

basis of McClendon's analysis of the iodine content of ocean water (50 parts per billion).<sup>5</sup>

Although the iodine together with the common salt is brought to the surface mainly by artesian wells and springs, many of these springs have become impounded

TABLE 1 IODINE AND CHLORINE<sup>6</sup> CONTENT OF MINERAL WATERS IN KANSAS (parts per million)

| Locality      | Chlorine | Iodine | Locality       | Chlorine | Iodine |
|---------------|----------|--------|----------------|----------|--------|
| Abilene       | 110,000  | 6.3    | Rosedale       | 14,000   | 1.0    |
| Arkansas City | 19,000   |        | St. Paul       | 17,000   |        |
| Atchison      | 16,000   |        | Greenwood Co.  | 6,900    |        |
| Eureka        | 4,390    |        | Allen Co.      | 16,700   |        |
| Fredonia      | 49,000   | 8.4    | Wyandotte Co.  | 25,700   |        |
| Genda Springs | 11,000   |        | Meade Co.      | 42,800   |        |
| Independence  | 45,000   | 1.3    | Douglas Co.    | 49,700   |        |
| Lawrence      | 30,000   |        | Barton Co.     | 54,500   |        |
| Leavenworth   | 16,000   |        | Pawnee Co.     | 57,800   |        |
| Marion        | 35,000   |        | Montgomery Co. | 59,400   |        |
| Mound City    | 10,000   |        | McPherson Co.  | 187,000  |        |

TABLE 2 IODINE IN DRINKING WATER (parts per billion)

| Permian salt area  | Points in surrounding states |
|--------------------|------------------------------|
| Lincoln, Neb.      | 0.05                         |
| Independence, Kan. | 0.06                         |
| Hutchinson, Kan.   | 0.10                         |
| Lawrence, Kan.     | 0.10                         |
| Fort Scott, Kan.   | 0.66                         |
| Kansas City, Kan.  | 1.69                         |
| Salina, Kan.       | 3.91                         |
| Ames, Iowa         | 0.012                        |
| Iowa City, Iowa    | 0.015                        |
| Bozeman, Mont.     | 0.015                        |

TABLE 3 FREQUENCY OF LARGE GOITERS PER 1000 DRAFTED MEN IN WORLD WAR I

| States containing Permian salt | Surrounding states |
|--------------------------------|--------------------|
| Texas                          | 0.30               |
| New Mexico                     | 0.88               |
| Oklahoma                       | 0.72               |
| Kansas                         | 1.25               |
| Nebraska                       | 2.14               |
| Colorado                       | 5.29               |
| Wyoming                        | 15.37              |
| Montana                        | 21.00              |
| South Dakota                   | 4.09               |
| Iowa                           | 6.68               |
| Missouri                       | 3.99               |

and form 'alkali lakes' over the axis of the salt deposits. Salt has been commercially obtained in the Texas Panhandle and Kansas for a long period.

<sup>1</sup> McCLENDON, J. F. and W. C. FOSTER. *J. Clinical Endocrinology* 1: 187 1941.

<sup>2</sup> McCLENDON, J. F. Iodine and the Incidence of Goiter. University of Minnesota Press, 1939. P. 8.

<sup>3</sup> MANSFIELD, G. R. *Indust. & Engin. Chem.* 15: 494 1923.

<sup>4</sup> SMITH, H. I. *Indust. & Engin. Chem.* 30: 854 1938.

<sup>5</sup> McCLENDON, J. F. *Science* 56: 269 1922.

<sup>6</sup> The University Geological Survey of Kansas. 7. Mineral Waters 68 1902.

The analyses of these springs (mineral waters) in Kansas for chlorine and iodine are given in table 1.

The chlorine content of the water supply of 146 cities and towns in Kansas averages 68 parts per million whereas in rivers not draining petroleum-salt regions it seldom exceeds 10 parts per million. The Pecos river drains the lower part of the Permian salt area and furnishes the main volume of the Rio Grande river at Laredo, which analyzed 164 parts of chlorine per million. The Arkansas river which drains Kansas averages 203 parts of chlorine per million at Little Rock. The Colorado river of Texas that drains the border of the Permian salt area averages 59 parts of chlorine per million at Austin. The Red River that drains the Texas Panhandle averages 121 parts per million at Shreveport. It is probable that all but about 10 parts of chlorine per million of these rivers came originally from Permian deposits and should contain the iodide occluded by the chloride.

Although the iodine analyses of drinking waters are few, the data in table 2 show a difference between the waters of the Permian salt area and that of surrounding states.<sup>2</sup>

The distribution of simple goiter in the Permian salt

area compared with that of the surrounding region necessitates the omission of the southern part of the latter since this southern region was entirely submerged under the sea during several geological periods. With this omission, the number of large goiters per 1000 drafted men<sup>7</sup> during the first world war is shown in table 3.

It seems evident that there is less goiter in areas over the Permian salt deposits than in the surrounding states and this is inversely correlated with the leakage of the deposits (specifically chlorine and iodine) to the surface. This adds support to the iodine-deficiency theory for the origin of goiter but it does not demonstrate that the iodine intake is adequate by individuals living over the Permian salt area, because the incidence of goiter is not zero. The universal use of iodized salt is recommended.

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<sup>7</sup> LOVE, A. G., AND C. B. DAVENPORT: Defects Found in Drafted Men. Gov. Printing Office, 1926. P. 111.

## Conservation of Scholarly Journals

THE AMERICAN Library Association has created a Committee on Aid to Libraries in War Areas, headed by John R. Russell, the Librarian of the University of Rochester. The Committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

One of the most difficult tasks in library reconstruction after the first World War was that of completing foreign institutional sets of American scholarly, scientific, and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the Committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. As far as possible they will be completed from a stock of periodicals being purchased by the Committee. Many more will have been broken through mail difficulties and loss of

shipments, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the Committee already give evidence that it will be enormous.

With an imminent paper shortage attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the Committee hopes to enlist the cooperation of subscribers to this journal in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project should be directed to Wayne M. Hartwell, Executive Assistant to the Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, New York.



## Abstracts of

# CURRENT CLINICAL LITERATURE

Editor DANIEL A MCGINTY Collaborators E B ASTWOOD, ISRAEL BRAM, JOHN C BURCH, JOHN C DONALDSON, MURRAY B GORDON, E C HAMBLIN, FRANK A HARTMAN, R G HOSKINS, J E HOWARD, ALLAN T KENYON, J T LEWIS, JOSEPH M LOONEY, A E MEYER, C A PFEIFFER, EMMERICH VON HAAM

## ADRENALS

LEWIS, R A, G W THORN, G F KOEFF AND S S DORRANCE

The role of the adrenal cortex in acute anoxia *J Clin Investigation* 21 33 1942

Five hours of low environmental O<sub>2</sub> tension produced in animals (rat, rabbit, dog, monkey) a depletion of liver glycogen with persistence of normal blood sugar levels, except when anoxia was severe. Twenty four hours exposure resulted in a rise in blood sugar level, liver glycogen (except in dogs), and increased urinary N, P, Na, Cl, K. The adrenalectomized animal proved incapable of surviving similar low O<sub>2</sub> tensions, and showed no comparable blood or urine changes, save for a marked increase in K excretion. Treatment of the adrenalectomized animals with 11 dehydro 17 hydroxycorticosterone evoked responses similar to those observed in the normal animal. Human subjects showed a decrease in N excretion upon 5 hours exposure to low tensions. The initial phase of anoxia appeared to be accompanied by increased utilization of carbohydrate in the normal subject. Adaptation to prolonged exposure consisted in a rise in protein catabolism. Neither change appeared in the adrenalectomized preparation —H O H

RAAB, W

Adrenocortical compounds in the blood. Relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure. *Arch Int Med* 68 713 1941

Human blood contains adrenal hormonal compounds consisting of epinephrine and cortical sterols (adrenocortical compounds) and most normal persons showed a level within normal range, as determined by a modification of the colorimetric method of Shaw. Smokers were above the average. Little change in the level was occasioned by exercise in normal persons, in contrast to the marked elevation usually found in patients with essential hypertension after a short period of exercise. An abnormally high level was found in a number of persons with renal hypertension, with congestive heart failure and associated pulmonary edema and particularly in those with renal insufficiency with associated uremia. No clear relation existed between the level of the adrenocortical compounds in the blood and that of the blood pressure. There was a tendency toward a fluctuating mode of secretion of the

adrenal glands in essential hypertensive subjects, which could be elicited by physical exercise and probably by other stimuli. The phenomenon furthered the development of arteriosclerosis and resulting ischemia in the vaso motor centers of the brain and in the kidneys, in this way contributing to the two outstanding mechanisms of central and renal hypertension. Adrenocortical compounds probably exerted a damaging effect on the cardiac muscle, in view of the tendency of the myocardium to absorb and to deposit both epinephrine and cortical sterols —W C Hunter (courtesy Chem Abstracts)

RUSSELL, JANE A, AND A E SILHELM

Glyconeogenesis in kidney tissue of the adrenalectomized rat *J Biol Chem* 140 747 1941

The formation of carbohydrate from pyruvate and succinate is unimpaired in kidney tissue from adrenalectomized rats, but there is significantly less formed in the presence of dl alanine, l (+) glutamic acid and a keto glutaric acid. An important factor limiting the rate of glyconeogenesis after adrenalectomy is the rate of deamination of amino acids, but the results with a ketoglutaric acid indicate that it is not safe to assume the indifference of the tissues to the products of deamination of all amino acids. The experiment, will be continued using liver slices —A P Lofthrop (courtesy Chem Abstracts)

## ENDOCRINE GENERAL

BREMER, J L

Osteitis fibrosa localisata *Arch Path* 32 200 1941

Experiments on rats indicated that the general disease may be caused by long continued excess of estrogens probably acting through the parathyroid glands. The local cysts may result from a temporary excess of estrogens soon reduced sufficiently to permit renewed normal growth. In this case a small amount of the mesenchymal tissue which is the initial stage of the 'fibrosis' may be cut off within the bone and there undergo any of the changes met with in normal histogenesis, especially those leading to fibrous tissue and cartilage. This condition was reproduced experimentally. These enclosed masses might enlarge, erode vessels, degenerate and liquefy, giant cells might cluster round them as around a foreign body. They might remain dormant for years. As an unusual variant of this more solid type, the true bone cyst could result

from the rare combination of temporary excess of estrogenic or parathyroid activity with chronic internal pressure in a neighboring joint or bursa. The condition would then resemble almost exactly that encountered in the pneumatization of avian bones. Successful entry of a diverticulum of joint or bursa into the bone might depend on the presence of emergent blood vessels whose loose mesenchymal adventitia could afford a pathway through the dense outer layer of the periosteum. Attempts to reproduce experimentally the proper combination of these circumstances were not successful, but the possibility of such a combination should be considered in any attempt to explain the etiology of human solitary bone cysts.—J. L. Bremer.

FREED, S. C., AND E. LINDNER.

The effect of steroids of the adrenal cortex and ovary on capillary permeability. *Am. J. Physiol.* 134: 258. 1941.

Crystalline corticosterone, desoxycorticosterone and commercial adrenal cortex extract were tested for their effect on capillary permeability by Menkin's leucotaxine method. Corticosterone and adrenal cortex extract prevented the action of leucotaxine in increasing the permeability of capillaries. Desoxycorticosterone did not do this but often produced a slight increase in capillary permeability. Estrone, stilbestrol and progesterone failed to prevent the leucotaxine effect but produced an increase in capillary permeability when given alone. The ability of steroids to maintain life in adrenalectomized animals is not necessarily related to their effects on capillary permeability.—E. D. Walter (courtesy *Chem. Abstracts*).

GLEBOVA, M. S.

The importance of the chorion as regards internal secretion. *Bull. biol. méd. expér. U.R.S.S.* 7: 16. 1939.

In addition to considerable amounts of gonadotropic hormones, the fertilized human ovum contains a special ketogenic hormone which probably is identical with the "fat hormone" of the anterior lobe of the pituitary described by Anselmino and Hoffmann. This ketogenic hormone could not be detected in the chorions of hogs and cattle, which contain less and more variable amounts of gonadotropic hormones than human chorions. Tests for the ketogenic hormone were made by determining the content in ketonic substances of the blood of adult male rats. Toxicoses of pregnancy, especially persistent vomiting, are probably due to an increased production of the ketogenic hormone, not in the pituitary, as assumed by Anselmino and Hoffmann, but rather in the chorion.—M. G. Moore (courtesy *Chem. Abstracts*).

HEMPHILL, R. E., AND M. REISS.

Investigations into the significance of the endocrines in involutional melancholia. *J. Ment. Sc.* 86: 1065. 1940.

Endocrine study of 30 female patients, including 15 nulliparae, suffering from depressive illnesses associated with menopause or the involutional state indicated an approximate grouping into: a) pure hypo-ovarian, b) hypo-

ovarian combined with hypothyroidism, c) hypo-ovarian combined with hyperthyroidism (7 cases, 6 of whom had borne children), d) hypo-ovarian combined with hypo-adrenalism (8 cases). Studies were made of vaginal smears, gonadotropic hormone increase, together with follicular hormone, luteal hormone, and corticotropic hormone treatment. The intimate relationship of pituitary and thyroid through the thyrotropic principle is emphasized; the importance of adrenal insufficiency in certain types of involutional melancholia is stressed; and it is suggested that disturbances of the activity of the anterior pituitary are largely responsible for the protean characteristics of involutional melancholia—W. L. Wilkins (courtesy *Psychol. Abstracts*).

LUBIN, S., T. S. DREXLER AND W. A. BILOTTA.

Postpartum pyeoureteral changes following hormone administration. *Surg. Gynec. & Obst.* 73: 391. 1941.

Dilatation of the urinary tract in post-partum women regressed within the first week in half of the subjects. Pituitrin seemed to enhance regression, progesterone to delay it, stilbestrol had no effect. The small number of patients used and the individual variations during a period of rapid physiological adjustment necessitates a tentative attitude toward these data, a point well recognized by the authors.—A.T.K.

VON HAAM, E.

Recent progress in endocrinology. *Ohio State M. J.* 37: 625. 1941.

Recent advances are reviewed. Successful separation of the various pituitary hormones, the creation of radioactive I, the isolation of the Na factor in the adrenal cortex and the exploitative investigation of stilbestrol are considered outstanding contributions of practical importance for the medical sciences.—Ruth Berggren (courtesy *Chem. Abstracts*).

## GONADS

ALBRIGHT, F., ESTHER BLOOMBERG AND PATRICIA H. SMITH.

Post-menopausal osteoporosis. *Tr. A. Am. Physicians* 55: 298. 1940.

Estrin therapy is effective in restoring a positive Ca and P balance in females with post-menopausal osteoporosis.—M. L. C. Bernheim (courtesy *Chem. Abstracts*).

ALLEN, W. M.

The chemical and physiological properties, and clinical uses of the corpus luteum hormone, progesterone. *Bull. New York Acad. Med.* 17: 508. 1941.

A review of the present day knowledge concerning the corpus luteum hormone is presented. Its chemical properties and physiological effects in animals are discussed. Included is a brief survey of the clinical application to women of the various physiological properties of progesterone.—C. T. Kaylor (courtesy *Biol. Abstracts*).

## BIRCH, C L

Assay of the estrogenic hormone in hemophilic and normal male urine *Proc Soc Exper Biol & Med* 48 167 1941

By use of a standard biologic method, 252 assays were made upon the urine of 52 hemophilics and normal controls. Of determinations on hemophilic urine 17% were positive, 28% of the determinations on normal urine controls were positive. Estrus per positive rat in both groups was averaged 14 hours. Although the hemophilic group showed a lower per cent of positive reactions the variations in both were so great that the difference is probably not significant.—C L Birch

## BOYD, E M, J W CLARK AND W F PERRY

Estrogens and their effect on ciliated mucosa *Arch Otolaryng* 33 909 1941

A method is presented for assaying the effect of estrogenic substances on movements of cilia taken from the buccoesophageal mucosa of the frog, by measuring the time required for the cilia to carry a mustard seed 1 cm. Crystalline estrone, estril and estradiol, dissolved in 0.75 per cent NaCl solution, stimulated ciliary movement when given in minute doses and depressed it in large doses. The range of doses producing stimulation when applied topically was about  $7 \times 10^{-2}$  to  $2 \times 10^{-1}$  mg estrone per 100 cc saline solution,  $2 \times 10^{-3}$  mg estril, and  $7 \times 10^{-3}$  to  $2 \times 10^{-4}$  mg estril.—Dorothy A Meyer (courtesy Chem Abstracts)

## CALCAGNO, B

Ocular disturbances of the menopause treated with artificial estrogens *Semana med* 48 657 1941

Two cases are reported of severe edematous conjunctivitis associated with general menopausal syndrome. Diethylstilbestrol dipropionate was injected twice weekly at a dose level of 0.5 mg. Complete recovery with subsidence of the menopausal symptoms was obtained after short treatment.—A E M

## CANTILLO, E, AND C F SPERONI

Endocrinopathies I Sexual impotence caused by adrenal hypofunction *Semana med* 48 687 1941

Complete loss of libido and sexual potency was found in a 30 year old male, with concomitant symptoms were anorexia, alternating constipation and diarrhea, discomfort after meals, general lassitude and mental depression. Diagnosis of adrenal insufficiency was borne out by response to treatment which consisted in parenteral application of desoxycorticosterone acetate, vitamins B<sub>1</sub> and C, and a few doses of testosterone propionate. NaCl was given by mouth and the diet was kept low in K. Complete recovery was effected within 2 months.—A E M

## CATEL, W AND H SCHOTOLA

The relation between thrombocytes, menstruation and the corpus luteum hormone *Med Klin* 36 973 1940

The number of thrombocytes in the blood of normal

menstruating women shows a phasic course. Since the peak of the thrombocyte curve coincides approximately with ovulation and the lowest point with menstruation, an endocrine regulation of this process is assumed. The number of thrombocytes is not appreciably influenced by the follicular hormone in physiological dosage but is diminished by the corpus luteum hormone. This action may perhaps serve as a test for preparations with suspected corpus luteum hormone properties.—Ruth Berggren (courtesy Chem Abstracts)

## CORNER, G W

The rate of secretion of estrogenic hormones by the ovaries of the monkey, *Macaca rhesus* *Arch Internat de pharmacodyn et de therap* 66 79 1941

A tentative estimate of 0.02 mg per day of estrone by a 4 to 5 kg monkey is made. This is equivalent to about 0.3 mg per day for a human female. Clinical trials indicate secretion of about 0.42 mg per day in human females.—G A E (courtesy Biol Abstracts)

## COUNCELLER, V S

Ten years' experience in the management of cryptorchidism *J Urol* 46 722 1941

This paper deals largely with surgical methods. The author concludes "Hormonal therapy in cryptorchidism should be confined to a relatively few patients and then only if spontaneous descent seems improbable. It may be used with benefit in cases of hermaphroditism or hypogonadism"—Author's conclusions J C D

## CURTIS, A H

Theca cell tumors (thecoma) *Surg, Gynec & Obst* 73 481 1941

Well illustrated operative material containing a 'high amount of estrogen per gram of tissue' was obtained from a 52 year old female who was still menstruating freely. Report is of interest in view of the conception that the theca and not the granulosa cells are the source of ovarian estrogens.—A T K

## DIBLE, J H, AND C M WEST

A human ovum at the previllous stage *J Anat* 75 269 1941

Presumably the youngest human ovum recovered to date is described. Measurements included embryonic disc 0.1 by 0.02 mm, endodermal plate 0.14 by 0.016 mm, and amniotic cavity 0.04 by 0.09 mm.—H O H

## FRANK, R T

Diagnostic procedures in female sex endocrine problems *Univ Penna Bicentennial Conf Female Sex Hormones* 1941 33

The concentration of estrogenic hormones in the blood, except during pregnancy is 0.1 to 50, hence determination



must be made by bioassay. By determination of gonadotropic activity of the blood and urine, a balance between secretion and excretion may be obtained. Estrogens occur in the urine in both free and combined forms; only free estrogens have been found in the blood. Androgens have not been found in 40-cc. samples of blood; their bioassay in urine is performed by determination of the growth response after application to the comb of a 3-day chick. The bioassay findings in the following conditions are reviewed: normal menstrual cycle, amenorrhea, menorrhagia, menopause, ovarian tumors, pregnancy, hydatid mole and chorio-epithelioma and adrenal cortical carcinoma. Estrogen increases progressively in the blood from the 8th week of pregnancy until its termination, but drops to zero within 24 hours after fetal death.—J. S. Hepburn (courtesy Chem. Abstracts).

FOLLEY, S. J.

Effect of estrogens on lactation. *Lancet* 1: 40. 1941.

In addition to inhibitory effects on lactation, estrogens will exert a galactopoietic action, as reflected in increase in concentration of both fatty and non-fatty solids in the milk. This galactopoietic action is characterized by a lower threshold than that for inhibitory action. Hence small doses enrich milk, whereas larger doses inhibit its secretion. Dissociation of the two effects is more readily obtained with the natural estrogens than with diethylstilbestrol.—H.O.H.

GALANG, CECILIA T.

Preliminary studies on the menstrual cycle of Filipino women students. *Acta med. Philippina* 2: 325. 1941.

Data on age at menarche and the influence of several factors on the menstrual cycle were obtained for 446 girls between the ages of 10 and 17 years enrolled in the Physical Education classes in the University of the Philippines. In 21.55% the onset of menstruation occurred at the age of 12 years; in 34.47% at 13; and in 26.50% at 14. There appeared to be no differences in age at menarche which could be attributed to climate, but the samples on which the figures were based were small: 35.71% of the 112 students on whom the effects of indulgence in physical exercise were studied noticed no effect on their menstruation; 23.21% had increased flow; 14.28% had cessation of menses; 10.71% had the onset of succeeding menses hastened; 11.60% had the onset delayed; and 4.46% experienced diminished flow. Physical exercise was therefore concluded to have a variable influence on individuals, 'personal adaptation' being the controlling factor.—Courtesy Child Development Abstracts.

GRAY, L. A.

Progesterone in nervous tension states. *South. M. J.* 34: 1004. 1941.

"A series of 38 women with nervous tension states, probably of endocrine and psychiatric etiology, is reported. Relief of symptoms with no formal psychotherapy occurred in the majority of cases after intramuscular injections of progesterone."—Author's summary. J.C.D.

GREENBLATT, R. G.

Histologic changes in the ovary following gonadotrophic administration. *Am. J. Obst. & Gynec.* 42: 953. 1941.

The author substantiates his previous finding that the use of gonadotropins, of various sources, fails to invoke an orderly process of maturation, ovulation, and corpus luteum formation in patients with primary ovarian insufficiency. The hope is expressed, however, that ultimately proper dosage, timing and optimal hormone combination will lead to more promising results. The report is based upon 36 cases in which examination of the results of gonadotropin administration was made incidental to laparotomy.—H.O.H.

HALBERSTAEDTER, L.

The role of artificial menopause in the treatment of cancer of the breast. *J. Internat. Coll. Surgeons* 4: 435. 1941.

In defense of oöphorectomy as an auxiliary measure in treatment of mammary carcinoma, the author cites earlier clinical observations and more recent experimental work. Two cases are reported in which roentgen-ray or surgical castration appeared to have been of definite value.—H.O.H.

HEARD, R. D. H., AND M. M. HOFFMAN.

Steroids. IV. The fate in man of injected  $\alpha$ -estradiol. *J. Biol. Chem.* 141: 329. 1941.

A total of 250 mg. of purified  $\alpha$ -estradiol was administered intramuscularly to a normal male subject in order to ascertain the nature of the urinary excretion products. Recovered unchanged were 9.8 mg. (3.9%), while oxidized to estrone (isolated as such) were 16.2 mg. (6.4%). No estriol or  $\beta$ -estradiol was obtained. Thorough exploration of the urine by systematic fractionation and chromatographic analysis failed to separate any other compounds which could be recognized as estrogen metabolites. Isolated were the usual steroids of normal male urine, androsterone, dehydroisoandrosterone, etiocholan-3 (a)-ol-17-one, pregnane-3(a)-20(a)-diol, and cholesterol, together with very small quantities of 3 unidentified substances. The fate of the remaining 90 per cent of the hormone, inactivated in the body, is discussed.—Authors' summary.

HECKEL, N. J., AND C. R. STEINMETZ.

The effect of female sex hormone on the function of the human testis. *J. Urol.* 46: 319. 1941.

Three patients, aged 60, 69 and 72, were treated for prostatic symptoms with estradiol benzoate. They received totals of 1,400,000; 1,200,000 and 1,600,000 R.U. in 31½, 45 and 28 weeks. The spermatozoa count fell from about 1,000; 820 and 720 millions to zero. There was temporary stimulation of the breast tissue and loss of libido.—J.C.D.

HOWARD, J. E.

Chemical, physiological and clinical aspects of the androgens. *Bull. New York Acad. Med.* 17: 519. 1941.

A review of the appreciation of the physiology of the androgens in their application clinically to the human male is presented.—C. T. Kaylor (courtesy Biol. Abstracts).

JOHNSON, W O

Limitations of estrogen therapy *South M J* 30 1006 1941

In understanding the limitations of estrogen therapy and using these products properly, correct diagnosis and specific therapy given to individuals in the best possible state of health is essential. Some of the conditions treated by estrogen therapy, in which results have not been wholly satisfactory, have been reviewed and an appeal has been made to use organotherapy only as a specific therapy—*Author's abstract*

KEARNS, W M

Testicular transplantation Successful autoplasmic graft following accidental castration *Ann Surg*, 114 886 1941

Satisfactory results were obtained through scrotal autoplasmic transplantation of testis slices in a 23 year old patient. Criteria of functional activity were based upon prostatic gland maintenance and secretion, persistence of libido and of normal clinical and laboratory tests—*H O H*

KUNSTADTER, R H

The hormone treatment of cryptorchidism eight years' experience *Urol & Cutan Rev* 45 81 1941

In 8 years, 71 cryptorchids were treated by hypodermic administration of either chorionic or equine gonadotropin. Sixty five patients had previously received no form of therapy. Six had previously been subjected to surgery. In the former group, complete descent occurred in 45 (69.2%) partial descent in 7 (10.8%) and complete failure occurred in 13 (20%). Eighteen (27.7%) were unilateral and 47 (72.3%) were bilateral. Twenty seven (41.5%) were of a normal constitution, and 38 (58.5%) showed definite evidence of an endocrine disturbance. A definite correlation between endocrine dysfunction, bilateral cryptorchidism and successful hormone therapy was observed. The majority of failures occurred in unilateral cryptorchids of a normal constitution. Six patients received hormone therapy following unsuccessful surgery and this proved to be of value in 3 patients. Response to hormone therapy usually occurred with a total dose of 2,500 to 7,200 R.U. of chorionic gonadotropin and from 240 to 2,550 units of equine gonadotropin. A large percentage of testes undescended at puberty are sterile. Many patients present endocrine disorders that may not improve spontaneously. Some have psychosexual disturbances. It is suggested, therefore, that all boys with cryptorchidism should receive endocrine therapy between 8 and 12 years of age. The parents of all patients treated should be informed that in the event of unsuccessful treatment, surgical correction should not be delayed—*Courtesy Clin Abstracts*

LESSER, M A

The treatment of angina pectoris with testosterone propionate *New England M J* 226 51 1942

On the basis of the reported circulatory effects of testosterone propionate, the author was led to its use in the

management of angina pectoris. Favorable results were obtained in 24 patients who received 25 mg intramuscularly every 2nd to 5th day. The response on the part of 20 males appeared definitely more pronounced than in the 4 females—*H O H*

LIN, H A C

Treatment of gonococcal vulvo vaginitis by estrogenic suppositories *Chinese M J* 58 527 1940

Daily doses of 100 to 150 R.U. of the estrogens from pregnancy urine for 10 to 50 days gave satisfactory results—*B C P A*

LOFTIS, E

Purpura due to injection of estrogenic substances *Arch Dermat & Syph* 42 138 1940.

A case of purpura localized to the buttocks and thighs is presented. The etiologic agent was an estrogenic hormone which was being administered intramuscularly. On cessation of the administration of this substance the purpura disappeared—*(courtesy Allergy Abstracts)*

MACBRYDE, C M, D CASTRODALE, ELLEN LOEFFEL AND H FREEDMAN

The synthetic estrogen diethylstilbestrol—clinical and experimental studies (II) *J A M A* 117 1240 1941

In a series of 202 estrogen deficient cases, the authors found that diethylstilbestrol therapy gave subjective and objective relief in 85%. Poor results were obtained in 4%. They advise intermittent rather than continuous treatment and find that 0.3 to 0.5 mgm daily for 2 to 3 weeks each month is frequently sufficient. Liver function, blood and urine studies gave essentially normal results. On continuous treatment nausea occurred in 20% of the cases, but on intermittent treatment the incidence was only 8.6%—*C P*

MARKHAM, M J

The clinical use of testosterone propionate in benign prostatic hypertrophy *Urol & Cutan Rev* 45 35 1941

In 7 cases testosterone propionate produced moderate to marked relief of all the symptoms of prostatism. Testosterone propionate is definitely indicated in the treatment of the symptoms of benign hypertrophy of the prostate: (a) where operation involves a definite risk to the patient's life, (b) where the palliative operation of transurethral prostatectomy has been unsuccessful, (c) in mild cases where surgery is not urgent and the patient is completely unwilling to submit to any form of surgery—*Courtesy Clin Abstracts*

McCULLAGH, E P, AND R JONES

A note on the effect of certain androgens upon the red blood cell count and upon the glucose tolerance *Cleveland Clin Quart* 8 79 1941

Long continued androgen therapy in a case of eu-

nuchoidism resulted in a rise of 25% in B.M.R. during course of treatment, an increase in red cell count (4.16 pre-treatment level to a high of 5.64), with increase in Hb. and hematocrit. Decreased glucose tolerance has also been noted in similar cases. These effects subsided upon withdrawal of treatment.—H.O.H.

MENDEL, E. B., A. M. GOLDMAN AND A. CAIRE, JR.

Inhibition of lactation with stilbestrol. *Am. J. Obst. & Gynec.* 42: 528. 1941.

Stilbestrol was used in 55 cases to inhibit or stop lactation both before and after lactation had occurred. In the average cases, a total of 20 mg. was used in the non-engorged and 30 mg. in the engorged or lactating breasts. The end results of both procedures were satisfactory. Abscess formation in the engorged breasts, as well as excessive amounts of fluid by the intravenous route and prolonged lactation, seemed to necessitate an additional amount of drug therapy. Three cases of severe painful engorgement of the breasts in the nursing mother responded favorably to 10 mg. stilbestrol without inhibiting lactation. In 1 case of severe juvenile diabetes the administration of stilbestrol did not affect the insulin requirement.—Ruth Berggren (courtesy Chem. Abstracts).

MOORE, R. A., M. L. MILLER AND A. McLELLAN.

The urinary excretion of androgens by patients with benign hypertrophy of the prostate. *J. Urol.* 44: 727. 1940.

Critical study of the method showed that, in any given study, a procedure must be accurately standardized and rigidly followed. The important points are: complete acidification and hydrolysis of the urine within 24 hours; the use of boiling rather than autoclaving for hydrolysis; hydrolysis of the acidified urine in a constant volume; and extraction with at least 10 volumes of benzene. Each 3-day specimen was assayed by the colorimetric method of Oesting, using the Zimmerman m-dinitrobenzene reaction, and by bioassay in capons. With normal urine there is a satisfactory correlation of the 2 tests, but with urine from older men with disease of the prostate there is an evident increase of chromogenic substance which is not biologically active. The average, maximum, and minimum excretions of androgens, in the equivalents of I.U. androsterone per day, were: young men (20 to 35 years) 19.4, 25.3, 10.3; older men without benign hypertrophy, 9.0, 16.6, 6.1; older men with benign hypertrophy, 6.7, 15.3, 2.2. Interpretation of these findings must await further investigation.—R. Berggren (Courtesy Chem. Abstracts).

MOORE, R. A., M. L. MILLER AND A. McLELLAN.

The chemical composition of prostatic secretion in relation to benign hypertrophy of the prostate. *J. Urol.* 46: 132. 1941.

Chemical analyses of the prostatic secretion in dogs and in man before and after the infection of an androgen and an estrogen lend no support to the theory that benign

hypertrophy of the prostate is due to an excess of either hormone.—Authors' conclusions.

NATHANSON, I. T., R. B. MILLER, LOIS E. TOWNE AND J. C. AUB.

The close correlation of androgen and creatinine excretion in normal children. *Endocrinology* 28: 866. 1941.

In growing children of both sexes there is a close correlation between the excretion of the 17-ketosteroids and of creatinine. The correlation of these 2 substances is so close that it seems highly likely that there is a fundamental relationship between them. The most likely explanation appears to be that androgens have an influence on the muscle mass of the individual so that an increase in androgen formation would result in an increased muscle mass, and therefore an increase in the rate of creatinine excretion.—F. Saunders (Courtesy Chem. Abstracts).

NATHANSON, I. T., LOIS E. TOWNE AND J. C. AUB.

Normal excretion of sex hormones in childhood. *Endocrinology* 28: 851. 1941.

This study is based on 1100 determinations on 59 normal girls and 40 normal boys: 565 were for estrogen, 495 for 17-ketosteroids, and 40 for the follicle stimulating hormone of the pituitary gland. It was found that from ages 3 to 7 years both boys and girls excreted a small but constant amount of estrogen and 17-ketosteroids in the urine, no striking difference in the excretion rates becoming obvious until about the age of 9 or 10 years. About 1½ years before menarche, estrogen excretion became cyclic in girls and the intensity of these cycles gradually increased. There was no cycle in 17-ketosteroid excretion in either sex, but after 11 years of age boys had a higher excretion. It appears that sexual maturity of boys and menarche in girls marks the culmination of a gradual endocrine development which starts about 5 years before puberty and that about 1½ years before maturity an additional mechanism appears which leads to more rapid differentiation of sex characteristics and eventual complete metamorphosis.—Courtesy Child Development Abstracts.

PALMER, H. D., D. W. HASTINGS AND S. H. SHERMAN.

Therapy in involutional melancholia. *Am. J. Psychiat.* 97: 1086. 1941.

In 53 patients the endocrine changes of the climacteric seemed to be related to the onset of the psychosis in only 24%. Treatment of the group with stilbestrol had no detectable favorable effect upon the psychosis though in some cases amelioration of menopausal conditions was seen. In 10 cases of involutional melancholia in men relatively little benefit of the psychosis from testosterone was seen but some improvement occurred in 2 early cases. In 15 cases combined use of parathormone,  $\text{NH}_4\text{Cl}$  and  $\text{Ca gluconate}$  was without significant clinical effect on the psychosis. It was concluded that life-long restrictions of the personality and traits deeply rooted in the psychobiology of the individual are more significant than physiological factors in the etiology of involutional melancholia.—R.G.H.

## PINCUS G, AND W H PEARLMAN

Steroid excretion in cancerous and non cancerous persons II Urinary estrogens *Cancer Research* 1 970 1941

Samples of pooled urines from 2 sets each of cancerous and non cancerous males and females revealed by bio assay—(1) higher estrogenic activity in urine of non cancerous females, compared with that of cancerous female subjects, (2) lower estrogenic activity in the urine of non cancerous males than in that of cancerous males, because of higher titers of non ketonic fractions, (3) a higher estriol fraction in urine of non cancerous females than in comparable fractions of urine of cancerous females, (4) 'estradiol' fractions in the urine of cancerous males was higher than the corresponding fractions in non cancerous males. Implications are discussed—H O H

## SALMON, U J, S H GEIST AND A A SALMON

Effect of androgen administration upon pregnandiol excretion in cyclical women *Proc Soc Exper Biol & Med* 48 11 1941

The effect of androgen administration upon pregnandiol excretion was studied in 8 women. The androgens used were methyl testosterone (3 patients) orally, in daily doses of 50 to 100 mg (total doses of 1480, 2350, and 2800 mg), testosterone propionate in oil (3 patients) intramuscularly in individual doses varying from 50 to 100 mg (total doses 600, 1050, 1175 mg), and testosterone (500 mg) and testosterone propionate (5166 mg) by pellet implantation (2 patients). Doses of androgens found in previous studies to be suppressive (i.e., to cause suppression of pituitary gonadotropic hormone excretion—inhibition of ovulation and menstruation) when administered early in the cycle, resulted in the absence of Na pregnandiol glucuronide in the urine during the current cycle and led to suppression of the next expected menstrual period. In 1 patient 1175 mg of testosterone propionate, administered after the 9th day of the cycle, did not appreciably affect the excretion of the pregnandiol complex during the current cycle—U J Salmon (courtesy Biol Abstracts)

## SATTERTHWAITE, R W, JUSTINA H HILL AND ELIZABETH F PACKARD

Experimental and clinical evidence on the role of the 17 ketosteroids in prostatic carcinoma *J Urol* 46 1149 1941

The urinary 17 ketosteroids were determined for 15 patients with prostatic carcinoma, 10 of whom were subjected to bilateral orchidectomy. In these 10 clinical improvement was correlated with decrease in urinary titer. The average level in the 15 patients prior to therapy ranged from 2.3 to 12.6 mg per 24 hour sample, which is within the normal range for elderly men without prostatic disease. Maximal clinical improvement was obtained in 2 patients who post-orchidectomy had the largest drop in 17 ketosteroid titer, i.e., relief of pain, decrease in urinary obstructive symptoms, and drop in basic phosphatase to normal levels. The patient showing least clinical improvement showed the least change in 17 ketosteroid value, an

average reduction from 3.9 to 3.4 mg. In the remaining 7 cases in which orchidectomy was performed, the clinical improvement appeared correlated with the per cent decrease in 17 ketosteroid titer—H O H

## SAVITZ, S A, AND S CHARTOCK

The clinical application of an extract obtained from the animal prostate gland *Med Rec* 152 3 1940

Treatment of 20 patients suffering from chronic prostatitis with an isotonic extract of fresh beef prostate elicited sufficient response to encourage consideration of this substance as a therapeutic agent—H O H

## SCHOCKAERT, J A, G DELRUE AND J FERIN

Comparative activity of estradiol and dioxy diethyl stilbene on vaginal pH in women *Compt rend Soc de biol* 131 1309 1939

By a vaginal pH test stilbestrol given orally or parenterally proved neither so potent nor so uniformly effective as estradiol benzoate administered intramuscularly—E Cutuly

## SCHOCKAERT, J A, AND J FERIN

Endometrial changes induced in ovariectomized women by feeding estrogens *Acta brev Neerland* 11 184 1941

Castrate urine induces follicle ripening without luteinization in the immature mouse. In the hypophysectomized mouse, castrate urine and pregnyl (P U) together cause luteinization and follicle ripening. Luteinization is therefore the result of the activity of two substances, one stimulating the follicles and the other the development of the interstitial cells. Analogous effects with these two substances are observed in the testicle—M L C Bernheim (courtesy Chem Abstracts)

## SHUTE, E

Hormone management of the nausea and vomiting of early pregnancy *Am J Obst & Gynec* 42 490 1941

Thirty five patients with vomiting in early pregnancy, who had high blood estrogenic levels, received testosterone propionate 10 mg q 3 d, 80% were 'cured' and 14% 'greatly helped'. Fifteen similar patients with low blood estrogens were treated with estrogens 10,000 I U q 3 d, 73% were 'cured' and 20% 'much helped'—E C H

## SMITH, R E

The undescended testicle *Lancet* 747 1941

Undescended testicles associated with clinical herniae should be treated surgically, others should be given the chance to descend spontaneously at puberty. If they fail to do so operation should be performed without delay. A preliminary course of hormone therapy will not often cause descent, but will make operation easier. Under this treatment the testicle undoubtedly hypertrophies, as can be judged clinically, and coincident with this is an increase of the circulation, fragile spermatic blood vessels becoming able to withstand the strain of being stretched when the testicle is inserted into the scrotum. Usually one post

operative course of hormone therapy will cause the testicle to enlarge further and maintain its new position. Puberty is the ideal age for operation, for at this time there is an excess of gonadotropic substances in circulation. Most of the testicles which do not descend spontaneously will be found to be ectopic or to have anatomical obstructions.—*Courtesy Clin. Abstracts.*

SOULE, S. D.

Anhydro-hydroxy-progesterone in threatened abortion. *Am. J. Obst. & Gynec.* 42: 1009. 1941.

Sixteen of 20 cases of threatened abortion were maintained to term by oral anhydro-hydroxy-progesterone, in dosages up to 100 mg. per day, and hypodermic progesterone, 1 to 30 mg. per day. No toxic symptoms were noted. Of the 8 multiparae carried through, 5 had aborted at least once previously.—H.O.H.

SPENCE, A. W.

Preparations of testosterone in eunuchism and hypogonadism. *Quart. J. Med.* 9: 309. 1940.

The effectiveness of the preparations was demonstrated on 2 eunuchs and 4 patients by intramuscular injections of testosterone propionate, implantation of tablets, inunction of testosterone and of testosterone propionate as an ointment or tincture, and oral administration of methyl testosterone. Potency was established and secondary sexual characteristics developed. In several cases psychological disturbances disappeared; there were improved mental outlook and pugnacity, increased libido, muscular strength and growth of testes and prostate. The effectiveness of each preparation was demonstrated. The maintenance doses required to produce about a similar effect were: (1) testosterone propionate intramuscularly, 50 to 75 mg. per week, given in 2 or 3 injections, (2) daily inunction of testosterone propionate as an ointment, 32 to 49 mg. per week, (3) daily inunction of testosterone as an ointment, 17.5 mg. per week, (4) oral administration of methyl testosterone, 350 mg. per week in doses of 10 mg. 5 times a day. Free testosterone implanted as a 50 mg. tablet exerted its action for 8 to 10 weeks.—B. C. Russum (*Courtesy Biol. Abstracts*).

SPURT, H.

Cyclic changes in the mammary gland of the rhesus monkey. *Surg., Gynec. & Obst.* 73: 388. 1941.

The difficulties surrounding attempts to determine the nature of the human mammary cycle from biopsy specimens of diseased breasts and from autopsy material are cited. Whole mounts of the breasts of rhesus monkeys supplemented by histological study reveal premenstrual enlargement of the lobules with increased vascular engorgement occurring only in ovulatory cycles.—A.T.K.

TEAGUE, R. S.

The effect of estrogens on the microscopic appearance of the liver. *J.A.M.A.* 117: 1242. 1941.

Teague finds that the vacuoles in livers from rats treated with diethylstilbestrol are predominantly glycogen when

selectively stained. This deposition of glycogen is comparable to that produced by other estrogens, and hence he concludes that the synthetic substitutes do not produce a serious toxic effect on the liver.—C.P.

TWOMBLY, G. W., AND A. F. HOCKER.

Chorioepithelioma in the male, treated with pregnancy serum. *Surg., Gynec. & Obst.* 73: 753. 1941.

Chorioepithelioma of the testis of a 33-year-old male was carefully studied by endocrine assay and at autopsy. The pituitary gland showed an increase in basophil cells and degranulation of eosinophils characteristic of pregnancy with absence of gonadotropic material in the acetone-dried gland. Gonadotropic material on the order of 40,000 to 130,000 mouse units (M.U.) was excreted per day, increased to 440,000 M.U. per day by treatment with serum of pregnant women. Seventy-two hour urine specimens contained 533 to 1110 M.U. estrone, 11 to 90 M.U. estradiol, 60 to 80 M.U. estriol (methods of Smith and Smith). These quantities, higher than those of normal males are sufficient to explain the patient's gynecomastia. Seventy-two hours specimens gave 20 to 24 mg. androsterone equivalents per day (colorimetric method of Callow, Callow and Emmens), 3.1 mg. androsterone equivalents per day (chick comb after Dorfman). These are normal values. Two 48-hour specimens showed 11 to 16 m. of crystalline material probably free pregnandiol (Venning).—A.T.K.

WALTER, R. I., U. J. SALMON AND S. H. GEIST.

Amenorrhea due to tuberculous endometritis. Failure of estrogens and progesterone to induce uterine bleeding. *Am. J. Obst. & Gynec.* 42: 505. 1941.

A case is reported wherein a patient, aged 23 years, who was treated with 1,028,000 R.U. of  $\alpha$  estradiol benzoate given intramuscularly in oil, 860,400 R.U. of  $\alpha$  estradiol given orally and 120 mg. of progesterone, over a period of 14 months, failed to experience uterine bleeding. Suction curettage after therapy disclosed the existence of atrophy of the endometrium and tuberculous endometritis.—E.C.H.

V. WESSELY, F.

Synthetic estrogens. *Angew. Chem.* 53: 197. 1940.

A critical review of the synthetic estrogens, particularly the stilbestrols, of animal experimentation and therapeutic use. Sixty-one references.—W. F. Bruce (*courtesy Biol. Abstracts*).

WIESBADER, H.

Oral therapy with pregnenolone in functional uterine bleeding. *Am. J. Obst. & Gynec.* 42: 1013. 1941.

In 20 cases of functional bleeding, oral pregnenolone, in dosages up to 50 mg. per day, was well tolerated, with beneficial effects in 17 cases. In the 3 unresponsive cases (juvenile bleeding) 25 to 50 I.U. progesterone by injection stopped bleeding within 72 hours. Regular cycles were re-established upon suitable reduction of medication. Total effective dosages of pregnenolone ranged from 280 to 350 mg. in 50 mg. daily doses.—H.O.H.

WILKINS, L, W FLEISCHMANN AND J E HOWARD

Creatinuria induced by methyl testosterone in the treatment of dwarfed boys and girls *Bull Johns Hopkins Hosp* 69 493 1941

In 7 cases of dwarfism treated with methyl testosterone, 25 mg per day orally, N retention appeared within the first 3 days of treatment, and increased creatinuria within 10 days. This increase continued and reached a high level by the 2nd to the 5th month. Withdrawal of treatment resulted in prompt N equilibrium or deficit, with gradual decrease in creatinuria over a 16 to 26 day period — H O H

## HYPOPHYSIS

BICKERS, W

Shock from posterior pituitary extract *South M J* 34 112 1941

Shock from this cause is rare but its recognition is important since it yields quickly to adrenalin, while the ordinary post partum shock due to hemorrhage requires a transfusion. A case in which this type of shock occurred at the close of two successive pregnancies is reported — J C D

CONLEY, R M

Adamantinoma of the craniopharyngeal duct *Am J Dis Child* 61 6 1941

The case of a 6½ year old girl with an adamantinoma of the craniopharyngeal duct with resultant manifestations of marked cachexia and Levi-Lorain type of pituitary infantilism is reported. Microscopic examination of the pituitary showed invasion of the posterior lobe by tumor tissue. The anterior lobe was compressed. Medical treatment is of no avail in cases of dwarfism or adiposity caused by tumors in this area. The operative mortality is high. The literature, diagnosis and treatment are discussed in detail — M B G

EVANS, H M

Growth hormone of the anterior lobe of the pituitary gland *J A M A* 117 287 1941

Growth hormone of anterior pituitary is discussed under the following headings: 1 Tests for regulation of growth by hypophysis; 2 Discussion of bioassay methods; 3 Growth promoting preparations; 4 Metabolic effects of growth hormone; 5 Relation of anterior pituitary growth hormone to other hormones; 6 Clinical use of extracts containing growth producing substance — C P

FARR, L E

Minimal nitrogen requirements of children with the nephrotic syndrome. Effect of the administration of a growth promoting anterior pituitary extract *Am J Dis Child* 60 1324 1941

The administration of a growth promoting extract of the anterior pituitary had no effect on the N assimilation of 3 nephrotic children. Intramuscular injection caused local reactions not observed when the same extract was given to other types of children — M B G

FERGUSON, J K W

A study of the motility of the intact uterus at term *Surg Gynec & Obst* 73 359 1941

Ferguson confirms the previous studies of Haterius and Ferguson to the effect that electrical stimulation of the pituitary stalk of the post partum cat or rabbit induces contractions of the uterus. This occurs when neck tissue is crushed leaving only carotid and jugular connections between head and trunk intact. This is interpreted as due to the liberation of an oxytocic hormone from the posterior lobe. Although slight elevations in blood pressure occur, there is no evidence that these are responsible for the observed changes. Evidence is presented that dilatation of the uterine horn and cervix evoke oxytocin secretion reflexly and that dilatation of the vagina only occasionally does so but more consistently induces complex reflexes serving to delay uterine evacuation while the vagina is occupied — A T K

FINLAY, J, AND M MAGIOAY

Blood sugar in a case of complete hypophysectomy *Arch Int Med* 68 893 1941

The total removal of the hypophysis in a 33 year old male produced a drop in the fasting blood sugar to hypoglycemic levels. No shock accompanied these low values. Sugar tolerance curves were somewhat erratic, with a tendency to a delayed rise and, at times, a plateau. The level of the blood sugar was not wholly dependent on the pituitary gland. The pituitary gland functions as a blood sugar level raising mechanism. The pituitary gland is not a vital organ — I B

FRASER, R, AND PATRICIA H SMITH

Simmonds' disease or panhypopituitarism (anterior). Its clinical diagnosis by the combined use of two objective tests *Quart J Med* 10 297 1941

The insulin tolerance test in 10 cases of suspected Simmonds' disease revealed a normal initial fall but a protracted recovery of blood sugar level. Myxedematous patients, on the other hand, showed a slow initial fall (inulin resistance). Urinary 17 ketosteroid assays proved essentially negative, 4 cases of anorexia nervosa gave positive values. Combined use of the tests will differentiate panhypopituitarism from allied syndromes. Insulin tolerance distinguishes primary myxedema, anorexia nervosa is differentiated by a positive 17 ketosteroid assay — H O H

FREUD, J, AND E DINGEMANSE

Augmentors for certain pituitary gonadotropins *Acta brev Neerland* 11 37 1941

There are 5 groups of augmentors for pituitary gonadotropins: (1) the chorionic gonadotropin of pregnancy urine, (2) the sulfates of Zn, Cu, Fe and Na, also ZnCl<sub>2</sub> and K soaps, (3) mucilaginous substances such as agar-agar, tragacanth, gum arabic and glycogen, (4) the Na salts of the bile acids and (5) gelding pituitary extract. Each augmentor can increase, at least 5 times, the gonadotropic effect of pituitary extract in young rats — M L C Bernheim (courtesy Chem Abstracts)

GERNES, L.

Amounts of serum of gonadotropic hormone in normal and pathological pregnancy. *Compt. rend. Soc. de biol.* 132: 111. 1939.

Numerous studies on the serum level of gonadotropic hormone were made in cases of fetal retention after death, pernicious vomiting of pregnancy, mole, and various stages of normal pregnancy. The values were quite variable and there was considerable overlapping.—E. Cutuly.

GREENBLATT, R. B., AND E. R. PUND.

The Gonadotropine: A clinical and experimental study. With observations on the use of a new gonadotropic mixture and on combined equine and chorionic gonadotropin administration. *South. M. J.* 34: 730. 1941.

Eight cases of functional amenorrhea received gonadotropin therapy. The results were assayed through clinical observation and endometrial biopsies. When menstrual bleeding occurred it was usually from an estrogenic endometrium. In 7 bitches, known to be in anestrus, receiving gonadotropins, 2 came definitely into heat and the rest showed some signs of active estrus. From the above series and other observations, the authors conclude in part "Evidence is presented that makes it difficult to believe that in functional or primary amenorrhea the gonadotropins can stimulate the subthreshold ovary to ovulation and corpus luteum formation in spite of the clinical improvement of the patient. . . . The presence of pregnandiol glucuronide in the urine following gonadotropin medication, at a time when none is expected, and the appearance of false progestinal responses of the endometrium do not indicate ovulation and corpus luteum formation, but probably reflect the luteinization of atretic follicles or corpora atretica of the ovary as the result of medication." The work on bitches "leads one to believe that the gonadotropins can stimulate the normal ovary, at least in normal bitches, during the non-receptive stage. A new gonadotropic mixture containing a synergistic factor from the anterior pituitary and chorionic gonadotropin evoked responses in the normal human ovary similar to those obtained following pregnant mares serum or extract of the anterior pituitary. Bleeding could be induced with more regularity following combined administration of equine and chorionic gonadotropins than when either were administered alone, but bleeding, except in rare instances, occurred from an estrogenic endometrium." —J.C.D.

PASQUALINI, R. Q., AND E. ETALA.

The hypophysis and NaCl excretion *Rev. Soc. argent. de biol.* 17: 198. 1941.

The effect of pitressin on diuresis and NaCl excretion was studied in 14 normal subjects. Excretion of NaCl varied in the same sense as the excretion of water; it was not influenced by pitressin. In 2 cases of diabetes insipidus no relation was seen between the excretion of NaCl, polyuria and injection of pitressin. The fact that water is reabsorbed by the renal tubule before NaCl, which is

only reabsorbed in the distal part of Henle's loop, serves to explain the regulation of the water and salt metabolism. —J. T. Lewis.

SELYE, H.

Effect of hypophysectomy on morphological appearance of kidney and on renotropic action of steroid hormones. *J. Urol.* 46: 110. 1941.

Female albino rats in groups of 6 or more were used, with similar groups as normal and operated controls. Progesterone desoxycorticosterone, testosterone, luteinizing hormone, follicle stimulating hormone, and the last two in association with testosterone were injected. They were given in quantities that were greater than that sufficient to give definite physiological effects on the sex organs. These hormones each had a growth stimulating effect on the kidney regardless of whether the animal was hypophysectomized or intact. In no case, however, were any of the hormones or their combinations used capable of completely overcoming the shrinkage of the kidney which follows hypophysectomy. The author concludes that the renotropic action of the steroids tested is not mediated through the hypophysis. The article contains a general review of the literature to date and 110 references.—J.C.D.

WADSWORTH, R. C., AND C. McKEON.

Pathologic and mental alterations in a case of Simmonds' disease. *Arch. Neurol. & Psychiat.* 46: 277. 1941.

A case of Simmonds' disease is presented which appeared after childbirth and was associated early in the course of the illness with a manic-depressive psychosis. The pituitary gland showed a unique, progressive, non-specific granulomatous process resembling allergic necrosis. There was secondary atrophy of the thyroid, adrenals, parathyroids, ovaries, uterus and breasts. These atrophic processes were accompanied by the development of marked cachexia and microsplanchnia. Scattered focal lesions observed in the central nervous system are attributed not to the psychosis but to the repeated attacks of hypoglycemia. Degenerative lesions in the supra-optic and paraventricular nuclei of the hypothalamus are thought to be secondary to destruction of the anterior lobe of the pituitary gland.—Authors' summary (R.G.H.)

## PANCREAS

BARNES, C. A., T. D. CUTTLE AND G. G. DUNCAN

Histone zinc insulin—its pharmacologic characteristics and its application in the treatment of diabetes mellitus. *J. Pharmacol. & Exper. Therap.* 72: 331. 1941.

The comparative effects of identical doses of histone zinc, unmodified, crystalline, and protamine zinc insulin were observed under strictly controlled conditions in 12 diabetic patients and in 1 nondiabetic subject. The hypoglycemic effects of unmodified and crystalline insulin disappeared between 6 and 8 hours after administration, whereas those of histone zinc insulin subsided in 18 to 22

hours, and those of protamine zinc insulin between 24 and 36 hours. The blood sugar lowering effect of histone zinc insulin was less abrupt and more prolonged than that of unmodified and crystalline insulin but more prompt than that of protamine zinc insulin. These qualities make it possible to secure a continuously normal blood sugar level and a freedom from glycosuria in a larger number of patients after a single injection of histone zinc insulin than is possible when other preparations are employed — Author's summary

#### BARNES C A, T D CUTTLE AND G G DUNCAN

Histone zinc insulin, its pharmacologic characteristics and its application in the treatment of diabetes mellitus *J Pharmacol* 72 331 1941

In human diabetics the hypoglycemic effects of unmodified and crystalline insulin disappeared in 6 to 8 hours after injection, the effects of equivalent doses of histone Zn insulin subsided in 18 to 24 hours, and those of protamine Zn insulin in 24 to 36 hours — L E Gilson (courtesy Chem Abstracts)

#### BATES G, AND C WEISS

Delayed development of antibody to staphylococcus toxin in diabetic children *Am J Dis Child* 62 346 1941

The development of antistaphylolysin was studied ( $\alpha$ ) in the serum of 14 normal children and the titers compared with those of a similar group of diabetic children. There was a delay in the development of antibody after intradermal injection of staphylococcus toxin in diabetic children. A correlation was observed between the state of diabetic control and the antistaphylolysin response of a group of diabetic patients. Diabetic children whose disease was excellently controlled responded in antibody production much as normal children whereas those whose diabetes was poorly controlled showed a definitely retarded and diminished production of antihemolysin — M B G

#### CHASE, LILLIAN A

Diabetes mellitus problems of its control *Canad M A J* 44 250 1941

The mortality from diabetes increased in Canada from 12.1 in 1933 to 14 in 1937. The death rate is highest in Ontario and lowest in Saskatchewan. The author discusses the role of hereditary and constitutional factors in the pathogenesis of the disease and stresses the excellent clinical results obtained with protamine zinc insulin in combination with a suitable diet — H Selye

#### CONN, J W, AND ELIZABETH S CONN

Metabolism in hyperinsulinism I Quantitative studies of the variations in the rate of combustion of carbohydrate produced by alterations in the diet *Arch Int Med* 68 876 1941

In organic hyperinsulinism an enormous overconsumption of carbohydrates signals an average diet of carbohydrate, fat, protein. The rate is restored to normal levels by extirpation of islet cell tumor. Low carbohydrate diet

depresses the postabsorptive rate of carbohydrate oxidation to levels seen under similar intake in normal subjects. However, the blood sugar level falls to hypoglycemic levels. Such low carbohydrate feeding inhibits the rate of hepatic glycogenolysis. In all conditions studied excessive liberation of insulin seems to be involved — H O H

#### CONN, J W, AND ELIZABETH S CONN

Metabolism in hyperinsulinism II Effects of epinephrine on glycemic level and on combustion of carbohydrate *Arch Int Med* 68 1105 1941

In normal subjects and in those with organic hyperinsulinism the postabsorptive rate of carbohydrate combustion was not increased by dosages of epinephrine of sufficient magnitude to produce a prolonged hyperglycemia. The RQ, if affected at all, was slightly depressed. Combustion of carbohydrate was not affected by the average height of blood sugar level, of itself. While epinephrine had little effect, ingested dextrose evoked excessively increased combustion, especially in cases of organic hyperinsulinism. From the results epinephrine would appear a valuable adjunct to treatment of severe organic hyperinsulinism, since its use does not increase sugar combustion while at the same time some relief is afforded the process of hepatic glycogenolysis — H O H

#### CONN, J W, AND ELIZABETH S CONN

Metabolism in hyperinsulinism III Effects of adrenal cortical extract on blood sugar and on sodium and nitrogen metabolism *Arch Int Med* 68 1115 1941

Daily administration of 30 cc of adrenal cortical extract to a patient with organic hyperinsulinism produced no anti-insulin or blood sugar raising effects, although the potency of the material used was attested to by its influence on Na and N balance. The dosage level may be an important factor in the use of adrenal cortical substances in clinical work, since it is pointed out that on a weight basis, much larger dosages have been employed in animal experimentation — H O H

#### DANIEL, W A

A study of insulin tolerance and glucose tolerance tests on normal infants *J Pediat* 19 789 1941

Fasting blood sugar levels in a series of infants 2 to 22 months old revealed values of 52 to 95 mg % average 71.5, based upon 37 determinations. Insulin tolerance and glucose tolerance tests on 25 and on 12 subjects respectively demonstrated that while the former is a safe method, the low blood sugar values obtained render its value somewhat equivocal as a diagnostic aid. The considerable variations found in the glucose tolerance test give it a dubious significance when used on subjects under 2 years of age — H O H

#### DAUGHERTY, J A

Endocrine manifestations in diabetic patients *Pennsylvania M J* 45 229 1941

The case histories of 425 diabetics were studied to determine the incidence of endocrine disturbance. Only



case of hyperfunction of the pituitary body was seen in this series of cases. The diabetes was of severe type. In all cases of pituitary hypofunction, the diabetes was severe. This is entirely contrary to experimental diabetes in which hypofunction produces a mild form of diabetes. Hyperthyroidism occurring during the course of diabetes showed an increase in the severity of the diabetes and difficulty in control. Hypoglycemic reactions and acidosis occurred frequently. Cure of hyperthyroidism produces a stable diabetic state. There must be some disturbance of glycogen storage and metabolism in hyperthyroidism which would correlate the physiologist's point of view. However, in several cases where diabetes followed the occurrence of hyperthyroidism the diabetes was not a very severe type. Hyperthyroidism cannot be given as a very prevalent cause of diabetes mellitus. Hypothyroidism should therefore ameliorate the diabetic state, but the cases herein reported showed the opposite to be true. Thyroid extract helped to permit the control of diabetes with diet and insulin. Gonadal disturbances in the female definitely affect the course of diabetes. Hypofunction certainly seems to aggravate the diabetic state. The effect of endocrine disturbances on the diabetic state, as seen clinically, is similar to the effect of the state of nutrition, the level of the metabolic rate, body temperature, exercise, infections, and a multitude of other variables. The primary abnormality in diabetes mellitus is in the insular mechanism.—I. B.

#### EDITORIAL.

The insulin monopoly. *J.A.M.A.* 117: 112. 1941.

This editorial reviews the history of the patent rights to insulin and discusses the action of the government in bringing suit against the 3 United States manufacturers under the Sherman Anti-trust Act.—C.P.

GRIFFITHS, M.

The antagonism between insulin and posterior lobe pituitary extract. *J. Physiol.* 100: 112. 1941.

No satisfactory answer can yet be given to the question of the existence of a direct antagonism between insulin and posterior lobe extract.—E. D. Walter (courtesy *Chem. Abstracts*).

JACKSON, R. L., AND I. BARTH.

Effect of adding vitamin B complex to the diets of stabilized diabetic children. *Am. J. Dis. Child.* 62: 516. 1941.

This study was undertaken in 5 diabetic children to determine if addition of vitamin B complex to standard diets for diabetic patients would alter the insulin requirement. Thiamin, 2 to 3 mg. in the form of vitamin B complex was added to the daily diet with an adequate supply of insulin and blood sugar levels were studied. Two of the patients were then watched for 2 weeks without additional vitamin B. The ingestion of vitamin B complex in excess of the amounts obtainable in well planned diets did not change the insulin requirements of well controlled diabetic patients.—M.B.G.

LEE, R. H.

The ocular fundus in diabetes mellitus. *Arch. Ophthalmol.* 26: 181. 1941.

No changes were found in the fundus of patients below the age of 40. In one group every patient with marked retinal disturbance had, in addition to different degrees of sclerosis, some abnormalities of blood pressure, and in every case except 2 the E.K.G. showed myocardial degeneration. In patients beyond the age of 50 it is rare not to find retinal lesions of diabetes, and these were typical in 6 cases. In the majority of these the E.K.G. revealed pathologic change. In another group the E.K.G. revealed in almost every case pathologic changes in the heart and vascular system. However, the cases were evenly divided as to retinal changes. Sclerosis and hypertension were evident in every case. In 5 there were typical retinal lesions of diabetes. No changes in the fundus were found in 69% of the cases. Metabolic disturbance alone does not seem responsible for the retinal changes. In the majority of instances of diabetic retinitis there was associated arteriosclerosis, hypertension, nephritis or a combination of these, frequently combined with myocardial degeneration.—R. H. Lee.

LOEB, R. F.

The practitioner and problems of diabetes. *California & West. Med.* 55: 182. 1941.

When overnutrition is abolished in a community, the incidence of diabetes is decreased, and this suggests a possible relationship between exhaustion of insulin supply and diabetes.—M. L. Ilsey (courtesy *Chem. Abstracts*).

MASON, H. H., AND D. H. ANDERSEN.

Glycogen disease. *Am. J. Dis. Child.* 61: 795. 1941.

Five groups are listed: a) Glycogen storage disease of the liver (true Von Gierke's disease) due to a defect, probably congenital, in 1 portion of the enzyme system which performs the conversion of glycogen to dextrose and dextrose to glycogen. b) Glycogen storage disease of the heart and muscles. The defect is present in another part of the enzyme system. c) Cases associated with galactosuria—probably due to a defect in the enzyme system of the liver that converts galactose to glycogen. d) The excess deposition of glycogen is due to the secretion or administration of excessive amounts of insulin and the ingestion of large amounts of carbohydrate. e) Miscellaneous group. A case is reported with clinical and postmortem studies which place it in the 1st group.—M.B.G.

MAURIAC, P., L. SERVANTIE AND A. BARON.

Demonstration of hyperlipemia induced in diabetics. *Compt. rend. Soc. de biol.* 132: 145. 1939.

Micro-determinations were made in 6 diabetic cases to determine the extent of lipemia following a standard procedure of fasting and fat ingestion. The patients fell into 3 classifications: a) Negligible or no hyperlipemia due to faulty absorption, accompanied by a low fasting lipemia; b) Hyperlipemia and normal lipemia in individuals without

faulty nutrition, c) Normal or augmented fasting lipemia, or hyperlipemia always exaggerated, indicating decreased fat tolerance, occurring in grave conditions of diabetes — E Cutuly

MEYER, K A, L AMTMAN AND L PERLMAN

Islet cell tumors of the pancreas *JAMA* 117 16 1941

A comprehensive review of the literature on islet tumors is given. The criteria for differentiation between the organic type of hyperinsulinism and the functional type are discussed, and it is pointed out that tumors are not under nervous or hormone control and are continually secreting insulin. A complete case report with successful removal of the tumor is reported — C P

NELSON, W E

Diabetic children in non diabetic camp *J Pediat* 19 25 1941

Diabetic children receiving adequate medical treatment can be normally active and can be permitted to partake of physical activity within ordinary limits. When special camps for diabetic children are not available, such children may be admitted to established camps which have adequate health supervision — M B G

SOSKIN, S

The blood sugar: its origin, regulation and utilization. *Physiol Rev* 21 140 1941

This is a review article with a summary on the mode of action of insulin. Some of the subjects covered in the discussion are site of formation, gluconeogenesis from protein and fat, homeostatic mechanism in the liver, pancreas, anterior hypophysis, thyroid, adrenal cortex, and other factors in regulation and emergency mechanisms, significance of utilization versus oxidation, significance of the R Q as judged from determination in vitro on isolated tissues and attempts to measure carbohydrate utilization in intact and liverless animals — H R Getz (courtesy Chem Abstracts)

STADIE, W C

Fat metabolism in diabetes mellitus *Ann Int Med* 15 783 1941

Study of liver slices from diabetic cats showed abundant formation of ketones but neither the acetic acid nor sufficient  $O_2$  uptake predicted from the Knoop B oxidation hypothesis. The fatty acids oxidized all appeared as ketones. The multiple alternate oxidation hypothesis is in accord with the facts. The  $O_2$  uptake is accounted for by deamination of amino acids,  $CO_2$  formation and ketone formation, leaving no residuum for conversion of fats into glucose. Ketones are utilized efficiently by the diabetic organism (evidence given in detail) without insulin and without the necessity of simultaneous carbohydrate oxidation. Re-examination of the data from calorimetric studies on diabetics with ketosis does not confirm the view that ketosis occurs when the ketone-antiketone ratio of 2:1 is exceeded. Ketosis appears when the tissue metabolism is shifted so far to fat that the body's capacity to

handle fat derivatives (2.5 gm/kg/day) is overcome by the ketone producing mechanism — A T K

THADDEA, S, AND H HAMPE

Gonadal hormones and diabetes in the aged *Zeitschr f Altersforsch* 2 206 1940

In aged persons both impaired activity of the pancreas and gonadal insufficiency play important roles. In normal subjects following injection of 50,000 u Progynon oleosum or of Testoviron (25 mg respectively), the fasting blood sugar and the sugar level after injection of 10 u of insulin are unchanged. The same is true of patients with juvenile diabetes. The same procedure in aged persons results in fall in blood sugar level, and the influence of insulin is enhanced. Oral Progynon, 2 X 1000 u daily, or Testoviron for a longer period by subcutaneous injection (10 mg every other day) lowers blood sugar level, and carbohydrate tolerance is improved. In cases of gonadal insufficiency the urinary creatine is commonly increased, due to splitting of muscle glycogen. In elderly diabetics the high creatine output can be eliminated by sex hormone injection, which acts via the pituitary. Sex hormones apparently have a depressant effect upon the pituitary body in the aged — Leo Hess

WATERS, E T, AND C H BEST

The pancreas as an organ of internal secretion *JAMA* 117 852 1941

In this review of the association of the pancreas and its internal secretion with diabetes mellitus, insulin is discussed as follows: chemistry, standard, source, insulin content of pancreas under different conditions, secretion, administration, mode of administration, allergy, mode of action, resistance and sensitivity, and possible substitutes. The question of a second internal secretion of pancreas, such as lipocaine, is also discussed — C P

WHITE, G, AND E A HASARD

Retinopathy in diabetes *Canad M A J* 44 586 1941

The incidence of diabetic retinopathy increases with advancing age and is frequently but not invariably associated with cardiovascular renal disease — H Selve

## PARATHYROID

ALBRIGHT, F

The parathyroids—physiology and therapeutics *JAMA* 117 527 1941

In this glandular physiology and therapy review article the parathyroids are discussed from the standpoint of normal and pathological physiology, hypoparathyroidism, and primary and secondary hyperparathyroidism — C P

KAPLAN, D

Treatment of postoperative parathyroid tetany with ovarian hormones *Am J Surg* 55 131 1942

On the basis of a postulated relation between ovarian activity and Ca balance, and in view of the chemical simi-

larity between sex hormones and vitamin D, 2 patients were treated with estrogens, progesterone, or both. Alleviation of tetany symptoms was found, although no influence on serum Ca was noted. Relief was attributed to the effects on neuromuscular excitability.—H.O.H.

McLEAN, F. C.

Activated sterols in the treatment of parathyroid insufficiency. *J.A.M.A.* 117: 609. 1941.

In this review article the activated sterols are discussed under the following headings: effectiveness, chemistry, dosage, toxicity, mode of action, dihydrotachysterol, and vitamin D. As comment, the author concludes that vitamin D preparations are as potent and as free from danger as dihydrotachysterol.—C.P.

NELLER, J. L.

Osteitis fibrosa cystica (Albright). *Am. J. Dis. Child.* 61: 590. 1941.

The case of the syndrome described by Albright is reported in a 7-year-old boy with a history of marasmus in infancy, pigmented spots and frequent fractures. Roentgen evidence of fibrocystic disease was supported by results of biopsy. The blood and urine were normal on both chemical and microscopical analysis except for increase in blood phosphatase. A review of the literature on the subject is given. The author considers that multiple embryonic defects of multiple systems rather than a single one are the most likely causative factors.—M.B.G.

POWER, F. H., S. PEDERSEN AND W. G. MADDOCK.

Tetany following sodium chloride replacement therapy. *J. Pediat.* 18: 776. 1941.

Unusual findings in a 15-year-old boy are reported. Symptoms of tetany were absent in spite of a marked degree of alkalosis as indicated by plasma chlorides of 182 mg.%, and CO<sub>2</sub> combining power of 99 vol.%, and intestinal obstruction. Following operation salt in the form of Ringer's solution was given to correct the deficit. Tetany developed on the tenth post operative day after the return to normal of the plasma chloride, CO<sub>2</sub> combining power and serum Ca.—M.B.G.

STROCK, M. S.

The mouth in hyperparathyroidism. *New England J. Med.* 224: 1019. 1941

The frequency with which oral symptoms appear in hyperparathyroidism suggests that manifestations about the teeth and within the jaws are of value in recognition of the disease. The dental symptoms are visible or palpable tumors of the jaw, malocclusion or distortion of the normal arrangement of the teeth, cyst-like cavities of the jaws, diminished dental caries, osteoporosis, closely meshed trabeculae and absence of the lamina dura. The fact that, even in extreme cases of demineralization in hyperparathyroidism, caries does not increase is convincing evidence

that the resorption of C and P from mature teeth is possible by way of the blood stream. Disorders of the parathyroid gland should be further studied to throw light on the etiology of dental diseases.—(Clin. Abstracts).

## THYMUS

MORGAN, E. A.

The present status of the thymus gland in pediatric practice. *Canad. M. A. J.* 44: 41. 1941.

A brief review of the physiology and the clinical pathology of the thymus.—H. Selye.

## THYROID

ABELSON, S. M., A. G. BRODIE, I. P. BRONSTEIN AND S. I. SCHREIBER.

Muscular macroglossia. Five year observation with cephalometric and speech studies in a case of spontaneous resolution. *Am. J. Dis. Child.* 62: 624. 1941.

In 1937 the authors reported a case of muscular macroglossia and stressed the non-thyroid etiological basis for some types. They noted that idiopathic muscular macroglossia occurred in infants and small children, often in association with congenital anomalies of the genito-urinary and gastro-intestinal tracts. Observation for 5 years of this patient revealed a definite spontaneous reduction in size, without any thyroid therapy.—M.B.G.

AIRD, R. B.

Experimental exophthalmos and associated myopathy induced by the thyrotropic hormone. *Ann. Int. Med.* 15: 564. 1941.

Exophthalmos induced in the guinea pig by pituitary extracts is re-examined. Evidence is presented that the active fraction is thyrotropic and that hypertrophy and degeneration of the extraocular muscles accounts for proptosis as in the malignant exophthalmos in man. A.T.K.

BISGARD, J. D.

The relation of hyperthyroidism to hypertension. *Surg.* 115: 42. 1942.

Essential hypertension was found to exist in 8 per cent of 357 cases of hyperthyroidism (systolic pressure 210-170). Elevation of systolic pressure above the physiological level (150) was reported in 25 per cent of the cases. Two types of hypertension emerge in the blood pressure changes following relief of hyperthyroidism, (1) cases with established hypertension, wherein little change in systolic pressure follows, and (2) cases with so-called latent hypertension, in which the blood pressure falls to approximately normal levels. Arteriolar disease probably exists in both types, differing only in degree, being more advanced in type (1).—H.O.H.

# The Journal of CLINICAL ENDOCRINOLOGY

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## A Clinical Comparison of Three Commercial Estrogenic Prepara- tions<sup>1</sup>

### [[Practical Use of Estrogens]]

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State Hospital, Ypsilanti, Michigan

SINCE POTENT estrogens have been available for clinical use there has occurred a pressing need for careful assay of these preparations on the human. All estrogens are active so that in selection or use certain attributes have been stressed, namely (a), mode of administration, (b), cost, (c), promptness of action, (d), duration of action.

Among the estrogens available to the clinician here is no standard unitage to indicate their relative human potencies. Two commonly used preparations are estrone and estradiol benzoate. A separate and distinct international unit has been devised for each of these from which in turn their respective dosages are calculated. These international units consist of arbitrary weights of the crystalline materials without relation to their biological effects. No unit has been devised for diethylstilbestrol so that its unitage is sometimes based on its potency, which under certain conditions is two and one half times as great as that

of estrone, i.e. if estrone has 10,000 i.u. per milligram, diethylstilbestrol is calculated to have 25,000 i.u. per milligram.

A series of estrogens when assayed in terms of rat units may have an entirely different dosage potency ratio when assayed in terms of mouse units. Thus, Doisy (1) has shown that when alpha estradiol and estrone are given in three portions during a 9 hour period, the alpha-estradiol is nine times as active as estrone if rats are used. Yet, it is only two times as active if mice are used.

This species difference has been recognized by other investigators (2-6) in their efforts to determine more nearly comparable human dosages. The interpretation of the results reported by various investigators has been difficult because each has his own human assay method. Thus, they have been unable to make more than general statements concerning the relative merits of the different estrogenic substances.

Doisy (1), who with Allen devised the Allen Doisy rat unit for estrogens, states that since bioassay has served its purpose in guiding chemists to the preparation of pure estrogens, it should now be discarded, the products for therapeutic use labeled in

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metric units and their evaluation effected by the response of patients."

Therefore, since neither international units nor rat units allow selection on the basis of clinical potency we have tried to clarify the dosage of estrogens by making an objective comparison of the effect of three estrogens in a selected group of women.

#### PROCEDURE

The general procedure used in assaying estrogens on test animals was followed as closely as possible (7). For accurate assays upon which reliable com-

of age, were on the same diet, and were not having sexual intercourse or intravaginal treatment.

Ten days was chosen as the period of treatment, because this is the approximate duration of the follicular or proliferative phase of the menstrual cycle.

The vaginal smear technique as described by Shorr (8) was used in this study. The classification of vaginal smear stages which we have devised incorporates some of the features of classifications developed by other authors (9, 10).

Over 1,800 slides were examined in this study, all by the first author. The reliability of the classification

TABLE 1. CLASSIFICATION OF VAGINAL SMEARS

| Number | Stage                 | Leucocytes<br>per High<br>Power<br>Field | Deep Cells<br>per High<br>Power<br>Field | Vesicular<br>Nuclei per<br>High Power<br>Field | Pyknotic<br>Nuclei per<br>High Power<br>Field | Predominating<br>Color       |
|--------|-----------------------|--|--|--|---|------------------------------|
| 1      | Atrophic              | 8-30                                     | 2-20                                     | 0-10   | 0   | Blue                         |
| 2      | Atrophic-<br>early    | 2-10                                     | 0-2                                      | 5-20   | Occasional                                    | Blue    Green                |
| 3      | Early                 | 1-5                                      | Occasional                               | 15-25  | Occasional                                    | Green    Blue                |
| 4      | Early-<br>moderate    | 0-3                                      | Occasional                               | 15-25  | 2-3   | Green                        |
| 5      | Moderate              | Occasional                               | 0  | Ratio  |   | Green    Red                 |
|        |                       |  |  | 3:1  |   |                              |
| 6      | Moderate-<br>advanced | 0  | 0  | 3:2  |   | Green    Red<br>Red    Green |
|        |                       |  |  | 2:2  |   |                              |
|        |                       |  |  | 2:3  |   |                              |
| 7      | Advanced              | 0  | 0  | 1:3  |   | Red    Green                 |
| 8      | Advanced-<br>complete | 0  | 0  | 1:4-5  |   | Red    Green                 |
| 9      | Complete              | 0  | 0  | 0-Occasional                                   | All cells                                     | Red                          |

parisons may be based, the following points are important: a), the use of large numbers of patients as closely alike as possible and without demonstrable ovarian activity; b), a fixed period of treatment for all of the hormones compared; and c), the taking of vaginal smears at regular intervals.

The importance of using large groups of individuals in any biological research is obvious because of the inevitable presence of a few highly sensitive and highly refractory individuals. Eight groups of ten to fifteen women each were treated with the specific dosage of the estrogen in question. The use of women in the postmenopausal period is the most practicable way of obtaining uniformity in the subjects. In the patients studied no ovarian activity was demonstrable from the vaginal smears taken prior to the institution of therapy. The women, all mental patients at the Ypsilanti State Hospital, ranged from 55 to 70 years

is attested to by the fact that when 200 of the slides were reclassified after a 6-month interval, 75 per cent were read identically. Most of the inconsistent interpretations were of the immature smear types. The smears which ranged from stage 4 to 9 were identically reclassified in 90 per cent of the cases. Since stage 4 to 6 is the important end point of the study, this degree of accuracy was felt to be satisfactory. Smears were taken at twice-weekly intervals before, during and after treatment, until the vaginal epithelium of all patients had returned to the atrophic state.

The pH of the vaginal secretion was determined with each smear. The potentiometer with calomel cells and a quinhydrone electrode was used during the early part of the study. Since such wide variations were found among different patients to the same dosage of the same estrogen, the simpler nitrazene and

congo red indicator papers were used for the remainder of the study. Due to the wide variations measured by both techniques it was felt that vaginal pH was not an accurate criterion of estrogenic activity. This inaccuracy was likewise noted by Shorr (11).

The estrogens used in this study were alpha-estradiol benzoate, estrone and diethylstilbestrol.<sup>3</sup> The first two were given by intramuscular injection and the last by mouth.

The minimum amounts of the estrogens (given in

alpha-estradiol benzoate (intramuscularly) and 0.4 mg. of diethylstilbestrol (orally) are equivalent.

This study has shown that 1.0 mg. of estrone (intramuscularly), 0.42 mg. of alpha-estradiol benzoate (intramuscularly) and 0.5 mg. of diethylstilbestrol (orally) are comparable dosages when assayed by our procedure on the human subject.

With dosages of the three estrogens which produced similar smear changes on the 11th day of treatment little difference is noted in the promptness or duration of response.

TABLE 2 RESULTS OF CLINICAL ASSAY

| Estrogen                              | Manufacturer's Estimate of Daily Dosage for 10 Days |                     |           | Stage of Vaginal Smear Response on Day After Cessation of Treatment | Days After Cessation of Treatment Before Smear Returned to Atrophic Stage | Number of Patients |
|---------------------------------------|---|---------------------|-----------|---|---|--------------------|
|                                       | Milligrams  | International units | Rat units |   |   |                    |
| Diethylstilbestrol, orally            | 0.50  | 12,500              |           | 4-6   | 28  | 11                 |
|                                       | 1.00  | 25,000              |           | 5-6   | 29  | 12                 |
|                                       | 1.50  | 37,500              |           | 4-8   | 30  | 13                 |
| α Estradiol benzoate, intramuscularly | 0.33  | 20,000              | 2,000     | 4-5   | 22  | 12                 |
|                                       | 0.50  | 30,000              | 3,000     | 6-7   | 42  | 8                  |
|                                       | 0.83  | 50,000              | 5,000     | 6-8   | 44  | 13                 |
| Estrone, intramuscularly              | 1.00  | 10,000              |           | 4-6   | 29  | 12                 |
|                                       | 2.00  | 20,000              |           | 5-7   | 30  | 12                 |

the same daily dosage over a 10 day period), necessary to produce an estrous or midinterval vaginal smear (stage 4-6) in the middle 75 per cent of each group of patients on the day following cessation of treatment, were considered comparable.

## RESULTS

The observations of vaginal smear types shown in table 2 were all made on the day following the cessation of therapy, the day on which the peak effect was obtained with each dosage. In several patients the smear types were found to be the same on the 8th as on the 11th day of treatment, but in no case was the former higher. The range shown is that of the middle 75 per cent of the patients in each group.

It will be noted that the higher dosages of alpha-estradiol benzoate tended to show a more prolonged effect than the other groups. However, when the three preparations were given in comparable human dosages there was no appreciable difference in duration of effect.

Commercial claims lead the physician to believe that 1.0 mg. of estrone (intramuscularly), 0.17 mg. of

Table 3 illustrates the importance of basing the cost of estrogenic preparations on their human potency rather than on their rat or international unit potency.

TABLE 3 COMPARATIVE COST

| Estrogen             | Cost of Estrogen Based on Commercial Claim |         | Cost of Comparable Human Dosages |         |
|----------------------|--|---------|----------------------------------|---------|
|                      |  |         |                                  |         |
| Estrone              | 1.00 mg.                                   | \$1.25  | 1.00 mg.                         | \$1.25  |
| α Estradiol benzoate | 0.17 mg.                                   | \$0.42  | 0.42 mg.                         | \$1.07  |
| Diethylstilbestrol   | 0.40 mg.                                   | \$0.013 | 0.50 mg.                         | \$0.016 |

## DISCUSSION

Estrogens are used successfully in the human in a number of conditions associated with decreased ovarian activity. While the biochemistry of these substances after administration is poorly understood at present, they will continue to be used because they are effective.

The vaginal smear is a readily available index of estrogenic activity. Qualitatively, on the vaginal epithelium, the actions of the estrogens are indistinguishable. Some differences in estrogenic effects on other parts of the body may exist but they have not been proven to date.

Manufacturer's claims and costs have been based in large part on rodent vaginal epithelial changes

<sup>3</sup> The estrogens used in this study were supplied by the following manufacturers: alpha-estradiol benzoate (as Progyon B) by the Schering Corp., Bloomfield, N. J.; estrone (as Theelin) by Parke, Davis & Co., Detroit, Mich.; and diethylstilbestrol by the Upjohn Co., Kalamazoo, Mich.

Definite discrepancies are noted here, between units based on rodent and human response. Therefore, we feel that since patients are the recipients of estrogenic therapy, more regard should be given to human response.

#### SUMMARY

1. The assay of three commonly used estrogenic preparations: alpha-estradiol benzoate, estrone and diethylstilbestrol on a group of postmenopausal women has been studied by means of vaginal smear response.

2. Manufacturer's claims lead the physician to believe that 1.0 mg. of estrone, 0.17 mg. of alpha-estradiol benzoate and 0.4 mg. of diethylstilbestrol are equivalent.

3. On the human subject this study has shown that 1.0 mg. of estrone (intramuscularly), 0.42 mg. of alpha-estradiol benzoate (intramuscularly) and 0.5 mg. of diethylstilbestrol (orally) all produce the same results.

4. Diethylstilbestrol is far cheaper than the other two preparations by any method of assay.

5. Alpha-estradiol benzoate costs one-third as much as estrone according to manufacturing claims

but it is nearly as costly when based on human response.

6. No appreciable difference was noted in promptness or duration of response to dosages of the three estrogens which produced similar smear changes on the 11th day of treatment.

7. The inadequacy of using a unit scale based on rodent response when dealing with human beings is emphasized.

The authors wish to express their appreciation of the assistance given by Miss Helen McRea in preparing the slides for this study.

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# Assay in the Human Female of Synthetic Estrogen, 118B

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IT IS BECOMING INCREASINGLY WELL-KNOWN that the potency of estrogens, expressed in terms of biologic units as assayed in the laboratory, cannot be assumed to indicate the potency of estrogens in the human female. To avoid the confusion arising from the comparison of the activity of estrogens when determined by different laboratories and in different animals it has been suggested that therapeutic standards of estrogens be determined by assays in the human female (1). Several assays have been proposed using various criteria. One of us (2) has recently reported a technic for assay in women which uses the subjective relief of symptoms in menopausal patients as the indicator of estrogenic potency. In this method three dosage levels of estrogen are used, thus corresponding to the manner in which laboratory animals are assayed. The non specific factors which interfere with the testing of menopausal patients are eliminated as much as possible by the proper selection of patients, using only those who have moderate to severe symptoms and eliminating those in whom there may be doubt as to the origin of the symptoms. In addition, non specific factors associated with treating such patients are reduced to a minimum by the omission of suggestion, by changing of dosage without informing patients and by having one investigator evaluate the therapeutic response of all patients. The criterion of relief was based to a great extent on the amelioration of hot flashes, but changes in other conditions such as nervousness, depression and insomnia were also considered.

In this manner we have already assayed diethylstilbestrol and dihydrodiethylstilbestrol (hexestrol). The results indicate that diethylstilbestrol is approximately five times as potent as dihydrodiethylstilbestrol, the average minimal therapeutic dosages being for diethylstilbestrol 0.5 to 1.0 mg by mouth daily and for dihydrodiethylstilbestrol 2.5 to 5.0 mg by mouth daily.

We wish to report the assay in women of a syn-

thetic estrogen, 118B, a substance which has no chemical relationship to the stilbenes or the natural estrogens but which is claimed to be relatively active by oral administration<sup>1</sup>.

Patients complaining of moderate or severe menopausal symptoms were given at different times the daily dosage levels of 1.0, 2.5 and 5.0 mg of 118B. The initial dosage was administered for three weeks,

TABLE 1. RELIEF OF MENOPAUSAL SYMPTOMS FOLLOWING DIFFERENT DOSAGE LEVELS OF THE SYNTHETIC ESTROGEN 118B

| Daily Oral Dose    |          |                    |          |                    |          |
|--------------------|----------|--------------------|----------|--------------------|----------|
| 1 milligram        |          | 2.5 milligrams     |          | 5 milligrams       |          |
| Number of Patients | Response | Number of Patients | Response | Number of Patients | Response |
| 4                  | Negative | 3                  | Negative | 2                  | Negative |
| 7                  | +        | 9                  | +        | 2                  | +        |
| 17                 | ++       | 18                 | ++       | 8                  | ++       |
| 4                  | +++      | 8                  | +++      | 7                  | +++      |

at which time an evaluation of symptoms was made and which in table 1 is signified as 1+, indicating slight relief, 2+, satisfactory relief, 3+, complete relief. After the therapeutic response was evaluated the dosage level was changed and after three or more weeks the therapeutic response again was evaluated. This procedure was repeated the third time. The data in table 1 indicate the results.

From these results it can be seen that 1.0 to 2.5 mg daily of the synthetic estrogen 118B by mouth is a satisfactory therapeutic dose. This compares favorably with the average dose of diethylstilbestrol which is 0.5 mg to 1.0 mg daily. The relief of symptoms in patients after administration of 118B could not be distinguished from that obtained with the stilbenes or with the natural estrogens. Only three patients experienced toxic reactions. One patient received 2.5

<sup>1</sup> The synthetic estrogenic substance (118B) was supplied by Schieffelin and Company, New York, N. Y.



mg. daily and two received 5.0 mg. daily. The untoward symptoms of all three were slight or moderate nausea. This lack of toxic symptoms following the use of 118B offers a marked advantage over the use of diethylstilbestrol and hexestrol.

#### CONCLUSION

A daily oral dose of 1.0 to 2.5 mg. of the synthetic estrogen 118B will produce satisfactory therapeutic response in the majority of menopausal patients. At

the therapeutic level this estrogen is relatively free from toxicity.

We wish to express our gratitude to Miss B. Kretscheld, R.N., for her aid in this work.

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# Cyclical Endometrial Response to Prolonged Administration of Estradiol in the Castrate Woman

## [[Castration and Endometrium]]

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THE OCCURRENCE OF periodic hemorrhages in the course of prolonged treatment with equal and constant doses of estrogens in castrated women and female monkeys is an important experimental fact in the knowledge of menstruation. Werner and Collier (1) injected castrate women daily with 100 to 300 i u of estrone in a watery solution, for a period of several months. Periodic uterine bleeding occurred during the treatment. Hisaw (2), Corner (3) and Zuckerman (4) obtained the same result in castrated female monkeys injected with moderate doses (approximately 100 i u) of estrone daily for a year. Bleeding recurred at intervals of 5 to 7 weeks. When Zuckerman repeated the experiment (5) using larger doses of estrone, he found that bleeding did not occur during the period of one year in which the castrate monkey received 1000 i u of estrone daily. Bishop (6) described 'threshold' bleeding which occurred periodically in a castrate woman receiving 5000 to 6000 i u of estrone. Reynolds, Kaminester and Schloss (7) administered estradiol dipropionate parenterally and estradiol orally to a castrate woman for a period of 5 months. Bleeding occurred three times in this patient at intervals of 18, 28 and 68 days. Davis (8) observed the recurrence of bleeding in amenorrheic women receiving 1 mg of diethylstilbestrol daily, even during the period of therapy.

Previous study (9, 10, 11) has shown that the vagina of the castrated rat responds rhythmically to estradiol. The present investigation was undertaken to determine if the endometrium of the intact uterus of the castrate woman will show a rhythmic response to estrogenic stimulation. The case is of special interest in that it is difficult to find a castrate woman whose uterus has been conserved, and who is willing to take daily injections of estrogen for five months.

### CASE REPORT

The patient, E B., aged 45, had had a double

oophorosalphingectomy performed 14 years previously (for cystic ovaries) and had been amenorrheic since. The vaginal smear (fig 1) revealed 80 per cent superficial spinous cells, 20 per cent deep spinous cells, and numerous leucocytes. A biopsy specimen of the vagina was composed of a thin superficial epithelium and a deeper layer of 2 to 3 row of cells. No biopsy of the endometrium could be obtained.

On May 24, 1940, daily injections of 200 inter-

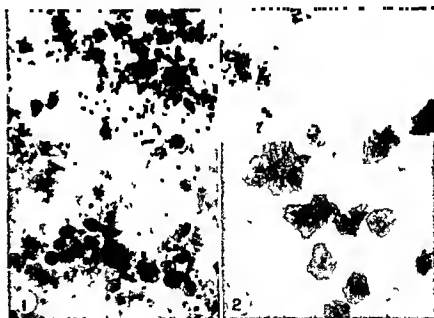


FIG 1 VAGINAL SMEAR BEFORE TREATMENT

FIG 2 VAGINAL SMEAR AFTER 6800 I U OF ESTRADIOL BENZOATE

national benzoic units of estradiol benzoate were begun. Fifty three days later, on July 17, the dosage was increased to 400 i u daily, and maintained at that level until December 14 of the same year.

During the period of treatment uterine bleeding occurred 4 times and lasted 2 to 5 days each time. The first period of bleeding appeared 60 days after the treatment was started, and the remaining periods were separated by intervals of 60, 32, and 29 days, respectively. Two days after the last injection profuse bleeding occurred.

Repeated biopsies of the endometrium revealed a state of proliferation and the development of glandu-

lar hyperplasia. Vaginal smears gave evidence of epithelial response to the estrogenic hormone (fig. 2). Figure 3 presents the data schematically.

#### DISCUSSION

The estrogen-withdrawal theory of menstruation (12) fails to explain the recurrence of bleeding from an endometrium under a sustained stimulation by injected estrogens. Allen, Hisaw and Gardner (13) sug-

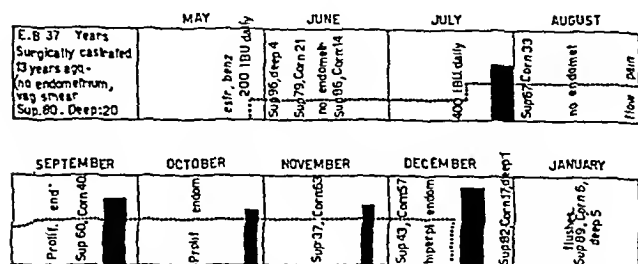


Fig. 3. CYCLICAL ENDOMETRIAL RESPONSE TO THE PROLONGED ADMINISTRATION OF ESTRADIOL IN THE CASTRATED WOMAN.

gested that bleeding from an endometrium under a continuous level of estrogen stimulus occurs when the amount of the proliferated endometrium becomes so great that the daily dose of 100 to 300 I.U. of estrogen is incapable of maintenance and thus the bleeding which occurs is the result of a relative estrogen deficiency. Such an explanation is plausible in cases in which watery solutions of estrone have been employed (1). However, if oily solutions of estradiol benzoate or dipropionate are used, absorption is slow, the effects are cumulative and the activity does not change over a period of time. Such preparations have been employed by Reynolds (7) and in our investigation, and the explanation of a relative deficiency is difficult to accept.

Previous experiments (9, 10, 11) have demonstrated that the vagina of the castrated rat periodically undergoes changes in its threshold of response to estradiol. The effect of acute adrenal insufficiency, injections of desoxycorticosterone and of progesterone on this threshold vaginal response was determined and the conclusion reached that "The vagina of castrated white rats possesses an intrinsic cyclical activity which is revealed by daily injections of adequate

doses of estradiol; it is abolished by progesterone and desoxycorticosterone, and not influenced by hypophysectomy."

The cyclical vaginal response can be demonstrated by the implantation of pellets of estrone (unpublished data). Zuckerman likewise has observed the cyclic response of the vaginal epithelium of the castrate rat. He introduced the concept that the threshold of response of the endometrium to estrogens shows periodic fluctuations; bleeding occurs when the threshold of endometrial response surpasses the level of estrogen, thus producing a relative insufficiency.

In summary, these experimental facts show that two mechanisms may explain the appearance of uterine bleeding, a), a variation in the concentration of estrogens in the organism with reference to its diminution or suppression (the estrogen-withdrawal theory), and, b), the periodic fluctuation in the threshold of the response of the endometrium even though the concentration of the estrogens in the organism does not vary.

#### SUMMARY

The case of a castrated woman treated for 5 months with daily injections of 400 I.B.U. of estradiol benzoate is described. Uterine bleeding appeared four times at intervals of 60, 32 and 29 days during the course of treatment.

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# Estrogenic Substances in Treatment of Pigmented Areas

## [[Estrogens and Pigmentation]]

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THE LOCAL effect of estrin, first demonstrated independently by Zondek (1) and Mussio Fournier (2) and later confirmed by a number of investigators, has been used in the treatment of certain diseases of the skin and mucosae. The results obtained in facial hypertrichosis, juvenile acne, vulvar pruritus and kraurosis bespeak the ability of the skin to absorb the estrogenic substances as applied either in greasy excipients or in alcoholic solutions. We have been able to verify a new local effect of such substances which we believe has not yet been reported in the literature. In the observation reported here the topical application of an ointment containing estradiol caused a number of facial pigmented patches to disappear in a female patient in whom they had already become of a less intense hue following the injection of estrin.

### CASE REPORT

The patient was an Uruguayan woman, married, aged 54 years.

**Personal history** Childhood, normal. Menarche at 15. The menses have always been regular and painless. Marriage at 16. Nine children, the youngest of which is 9

with a basal metabolic rate of minus 29 per cent. The patient's hypothyroid disturbances improved with thyroid, which she had for only two months.

She came under our observation in October, 1939, her chief complaints being cardiac, circulatory, and climacteric vasomotor disturbances. The patient still menstruated and no hypothyroid signs were present.

We realized presently that the patient had some facial brown-colored pigmented areas scattered around the eyes, at the eyebrows and in the superciliary region predominantly on the left side, as well as about the zygomatic regions and the cheeks (fig. 1). Similar patches were found on the left arm and on the lower portions of both forearms, and also about the hands and knees.

The most confluent and widespread patches were those on the face. Their form and distribution were irregular and the skin was smooth and thin at their level, normal in appearance and without manifestations of vitiligo. The patient stated she had had the patches on the face and forearms for a number of years. Seven years ago a derma-

tologist instituted electrocoagulation therapy, and since then discolored striae have been present on the cheeks. The patches had increased in number and size in the past year.

**Physical examination, October, 1939** Height, 154 cm. (5 ft.), Weight, 56 kg. (123 lb.) General health, good. The skin is thin and there is no dryness. The facies show a certain degree of puffiness. The presence of the pigmented patches and their distribution has been already indicated. The hair is dry, coarse and scanty on the scalp, some is gray. There is a thinning of the outer half of the eyebrows.



Fig. 1 FIFTY FOUR YEAR OLD PATIENT, OCTOBER, 1939

The eyes are brown and the sclera is blue. **Mouth** There are numerous caries and paradentosis. The mucosa is free from pigmentation. **Neck** The neck is thin and the thyroid gland is not palpable. No supraclavicular fat pads are present.

**Thorax** Lungs, normal sounds. Heart, normal. Pulse rate, regular and 72 per minute. Blood pressure, systolic 110, diastolic, 75 mm. Hg. Eczema is present on the anterior portion of the chest and submammary folds. **Abdomen** Viscera, not palpable. The vesicular region is tender. **Extremities** Negative findings upon examination with the exception of the pigmented patches already pointed out. **Neurological examination** No noteworthy findings recorded. The patient is of a quiet disposition. She mentioned sensitivity to cold and slight perspiration. There is no constipation. The appetite has diminished.

Sleep is normal, the memory poor. There is no asthenia. *Genitalia.* Normal in development. Irregular menses, with periods of amenorrhea of from 1 to 2 months.

*Laboratory findings.* Blood cholesterol, 219 mg. per cent. Blood urea, 20 mg. per cent. The Wasserman reaction was negative. Urine findings were normal. *Roentgenogram of the chest.* The heart and aorta are normal in appearance. *Electrocardiogram.* Normal tracings.

The histologic examination of a biopsy specimen of the pigmentation on the forearm showed the following charac-



Fig. 2. (left). PATIENT AFTER TREATMENT WITH ESTRADIOL subcutaneously over a period of 2 months followed by treatment with estradiol in an ointment for a period of 20 days. Fig. 3. (right). PATIENT IN FEBRUARY 1941 ONE YEAR AFTER CESSATION OF THERAPY.

teristics. The pigment lies in the basal layer of the epidermis, within the cells, where it adopts a polar disposition, predominantly toward the superficial pole. At the borders of the patch the basal layer suddenly loses its pigment and the basal cells appear free from it. There are no pigment granules in the Malpighian layers. Important changes are found in the corium. A lymphoid infiltration is observed in the midst of a dissociated tissue, a dissociation which is probably due to edema. There is perivascular infiltration together with alterations of the walls of the vessels, which are predominantly thickened, but without sclerosis. From this histologic examination, as well as from the lack of pigment in the dermis, it is inferred that these are pigmentary patches and not pigmented nevi.

*Treatment.* Estrin was prescribed (estradiol subcutaneously) at a dosage of 5000 I.U. twice a week, up to January, 1940. The patient's menses became regular and her subjective disturbances were relieved. The patches about her face turned to a lighter color. An ointment of estradiol containing 250,000 I.U. in 50 gm. of excipient was then applied to her face for 20 days. A few patches were observed to disappear, while others showed a rather lighter hue (fig. 2).

Both the local treatment and the injections were continued. In September, 1940, the pigmentation had noticeably diminished on the face as well as in many other parts of the body, although it persisted chiefly about the forearms and hands.

The local treatment with estrin and the injections of the same substance were discontinued. The pigmentation continued to improve and in February, 1941, the patches

on the face had completely disappeared (fig. 3). Although the patches on the forearms and hands still persisted, they were less marked than before. The patient has continued menstruating. At present (September, 1941) she presents small patches which have reappeared some time ago about the eyebrows. During this year she has received no hormonal treatment at all.

#### COMMENT

The appearance of pigmentary patches is not infrequently met with in the menopause, though they usually are not of such a dark color as in our case. It is also encountered in ovarian diseases and is a common sign during pregnancy. Marañón (7) has studied the influence of the pituitary gland on these dyschromias. Melanogenesis is inhibited through the sympathetic pathways, and, on the other hand, is stimulated by the hypophyseal melanophoric hormone. It is generally admitted that during menopause there is an increase in pituitary activity, as evidenced by the clinical signs and hormonal estimations. The ovarian deficiency would probably be the determining factor for this endocrinopathy. Among the consequences of this glandular imbalance is the disturbance of the pigmentary processes. The influence of estrin on melanogenesis concerns chiefly the normal distribution of the pigment. The effect of estrin on the pigmentation of the areola has been experimentally demonstrated by Lipschütz and other investigators (3, 4).

Zondek, (5) has been able to bring about an increase in the pigmentation of the areola by applying estrin locally.

Such results are positive only in those regions normally showing pigmentation, and, as Vilter (6) states, it has not been possible to induce pigmentation by means of estrin in other areas of the skin. On the contrary, and as we have verified in our patient, it is admissible that the estrin causes the disappearance of the abnormal pigmentation through a local effect on the melanocytes when it is applied on the skin or when it acts on the pituitary gland if used in injections, thus inhibiting the melanophoric hormone.

#### SUMMARY

The case is reported of a climacteric patient, to whom estrin was administered first locally and then by injection because of areas of pigmentation on the skin. Pigmentary patches on the face disappeared.

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# Association of Uterine Fibromyomas with Other Clinical Conditions

## [[Uterine Fibromyomas]]

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IN 1922 the simultaneous occurrence of tumors of the uterus, thyroid and breast was reported (1). In a series of 200 cases (100 uterine myomata and 100 goiters) fifty three patients, or 26.5 per cent, had both goiter and uterine myomata. Five per cent had breast tumors.

The present report is based on 410 cases of Caucasian women with uterine fibromyomas. The ages ranged from 22 to 55 years, the average age being 42 years.

Three hundred and forty-eight of the patients (85%) were married. Of these, 75 (21%) had never been pregnant, 84 (24.5%) had had one or more spontaneous miscarriages.

One hundred and twenty nine (37%) had migraine headaches. Two hundred and fifty three (63%) had a goiter. Of this number 83 (33%) had a subsequent thyroidectomy.

Of the 410 patients with uterine fibromyomas, 268 (65%) had a hysterectomy. Seventy-seven (18%) had radium therapy for the uterine fibromyoma. Since 268 had a hysterectomy there remains a balance of sixty-five (15%) who were neither operated upon nor had radium therapy. These procedures may have been carried out elsewhere.

One hundred and sixteen (28%) had some form of arthritis, the majority of cases being classified as osteoarthritis or hypertrophic arthritis.

Sixty (22%) of the 268 operated cases had in addition a cholecystectomy for cholelithiasis. An additional 23 of the remaining 142 not operated upon had evidence of cholelithiasis by the Graham dye method of study—a percentage of 16. The total of all cases having cholelithiasis, diagnosed either at operation or by roentgen ray study, was 83 (20%).

Three hundred and fifteen (75%) had one or more members of the immediate family who were 72 inches or more in height.

Blood pressure readings were made on 362 patients. These were as follows:

| Number of Cases | Percentage | Systolic Pressure mm Hg | Age Range Years | Average Age Years |
|-----------------|------------|-------------------------|-----------------|-------------------|
| 22              | 6.1        | 80-100                  | 30-48           | 38.0              |
| 103             | 28.1       | 100-120                 | 18-54           | 38.5              |
| 132             | 36.5       | 120-140                 | 19-60           | 41.8              |
| 64              | 17.7       | 140-160                 | 27-62           | 44.2              |
| 24              | 6.6        | 160-180                 | 33-55           | 45.1              |
| 17              | 4.6        | 180-270                 | 35-63           | 47.4              |

The systolic pressure ranged from a low of 80 to a high of 270 mm Hg, the average age of this group of 362 patients was 40.8 years.

Twenty-two (5%) of the 268 operated cases had a subsequent operation for intestinal obstruction. Twenty (5%) of the 410 patients had hearing defects. Twenty-two (5%) had mastitis. Twenty-four (5%) had tumors of the breast divided as follows: cystadenoma 10, adenocarcinoma 3, simple adenomas 11. The total number of patients with breast involvement was 46 (11%).

### COMMENT

The average age of 42 years for this series of cases corresponds with that of the series of Costolow (2) who reported the average age of 986 patients with uterine fibromyomas as being 42.5 years.

The majority of the patients (85%) were married and 21 per cent were childless. In the menstrual history of these women the fact was noteworthy that most of them stated that the cycle was irregular from the time of menarche. Periods of amenorrhea followed by menorrhagia was a common complaint, showing that a predisposition was present from the beginning of the menarche.

The high incidence of migraine headaches seems to be greater than is usually encountered in association with other diseases. In a series of 100 patients

with migraine 70 per cent of 51 female and 80 per cent of 21 male patients had one or more members of the immediate family who were 72 inches or more in height (3). The combination of familial tallness, migraine headaches and uterine fibromyoma may have some significance as indicating a common etiological factor.

The association of goiter with uterine fibromyoma has been noted by many others. Freund (4) found that of 56 women with uterine fibromyoma 44 (approximately 80%) had a goiter. V.Graff (5) in a study of 112 women stated that 31 (27.7%) had a goiter. Ségond (4) Ullmann (6), Fraenkel (7) and many others have noted the high incidence of this combination.

It is of interest that none of the goiters in this series was classified as belonging to the exophthalmic type. In diagnosing a goiter as adenomatous, the impression gained by palpation that it is nodular determines the clinical diagnosis. This diagnosis is subject to error and to be accurate requires the verdict of the pathologist, as well as of the surgeon at the time of operation. Of the 253 women with goiter, 83 (33%) had the goiter removed and the specimens were all reported as being adenomatous. The clinical impression, therefore, seems to be fairly accurate and one is safe in saying that a large number of women with uterine fibromyoma have a goiter, regardless of whether it is adenomatous in character or not.

It will be noted that this series of patients with uterine fibromyoma consists entirely of Caucasian women. It is a well known fact that Negro women have a much higher incidence of uterine fibromyoma than Caucasian Women (8-12). On the basis of the present data, as well as that of others, the incidence of adenomatous goiter in the colored race should be much higher than in the Caucasian. Such is not the case, however, and in fact the reverse seems true.

An explanation of this is purely a speculative anthropological problem. Elsewhere (13) it has been pointed out that the mesoderm of the Negro showed certain singular characteristics when compared with that of the Caucasian. This tissue in the Negro is particularly susceptible to disease whereas the ectoderm is relatively immune. The mesoderm gives rise to the tissues comprising the uterine fibromyoma. The close physiological relationship existing between the pituitary gland, the uterus and the thyroid is well-recognized.

Freeman (14) has shown that the Negro race has a heavier pituitary gland than the Caucasian if the pituitary weights of the same sexes are compared. If one assumes that the heavier gland in the Negro means more activity and therefore that it secretes an increased amount of thyrotropic hormone, then the lower incidence of goiter or thyroid enlargement in the Negro is puzzling. Of course glandular enlarge-

ment does not necessarily mean increased function, as witness the hypofunction of the goiter in cretins, and the chromophobe adenoma of the pituitary. However, the cellular morphology of the Negro's pituitary, as well as the clinical evidence, points to as great activity, if not greater, than that found in the Caucasian.

The influence of the thyroid gland on both the development and function of the ectodermal nervous system has been amply verified. The relative immunity to disease of the ectoderm in the Negro has been pointed out (13, 15). The development of the nervous system in the Negro is not as great as in the Caucasian considered in the higher sense of psychic and intellectual development. The Negro does not suffer from diseases of the nervous system in any comparable statistical frequency as compared to the Caucasian.

Is the relative immunity of the ectoderm in the Negro accounted for by the fact that thyroid disease is less frequent, or, put in another way, does the relative inactivity of the thyroid in the Negro account for the lack of nervous system involvement? In other articles (16, 17, 18) data have been submitted showing the embryohormonic relations of the thyroid gland to ectodermal tissues. Having a bearing on the present discussion of the lessened incidence of goiter in the negro, as well as the relative immunity of their nervous system is the following:

Davenport (19), speaking of the geographical distribution of multiple sclerosis as found in the recruits of World War I said: "The resemblance between the distribution of multiple sclerosis and chorea is considerable except that chorea is abundant also in Texas, Mississippi, Missouri and the states of the North Atlantic coast and of the eastern slopes of the drainage basin of the Ohio River. That is, high rates for chorea are more widespread than for multiple sclerosis. The resemblance of the distribution of multiple sclerosis to that of simple goiter is somewhat striking. In both diseases, comparatively few cases are found south of the Ohio River. The maximum rate is in Michigan, Wisconsin and the extreme Northwest. The Negro race is not immune to the disease; although as indicated it, including mulattoes, is probably less subject to the disease than the white race." In Davenport's table the percentage distribution of multiple sclerosis among injuries and diseases of the nervous system, as determined in certain classified races, showed that the African percentage was 3.5 in 511 cases of multiple sclerosis; only the Dutch, who had a percentage of 1.0, had a lesser incidence than the African. The Scandinavian race had the highest percentage, being 12.5; the French 10.7; Slav 9.0; German 8.3; Scotch 8.2.

Brain (20) states that multiple sclerosis is most prevalent in Northern Europe and Switzerland. The

latter country, as we know, is noted for its high incidence of goiter. Brain says that in England and Wales there are approximately 200 cases of multiple sclerosis per million living persons or 1 in 5000. In Switzerland the incidence is nearly double. This adds support to Davenport's observations that where goiter is endemic there multiple sclerosis seems to be more prevalent. The maximum rate for multiple sclerosis in drafted men was found in the states of Michigan and Minnesota, each having 18 per 100,000.

In my series of 410 uterine fibromyomas with 253 (63%) having goiters, there were 6 cases of multiple sclerosis. This would give a percentage of 1.46. Five of the 6 cases with multiple sclerosis had a goiter. In one family of a tall Swedish type, was one member who had a hysterectomy for a fibromyoma and a thyroidectomy for a toxic goiter. She died with multiple sclerosis which preceded the symptoms of fibromyoma by several years. Her brother also died with multiple sclerosis, the diagnosis in both instances having been confirmed in other institutions. One sister had a thyroidectomy for toxic goiter and another sister had a hysterectomy for fibromyoma and the latter also had a nodular goiter.

Another patient developed symptoms of multiple sclerosis at the age of 22 and had a hysterectomy at 34 for uterine fibromyoma. She died one year later from the complications of multiple sclerosis.

Davenport (19) in discussing the geographic distribution and race of those having multiple sclerosis said "Various hypotheses are suggested for these facts. One is that there is some race inhabiting the Great Lakes region and the State of Washington that is especially subject to multiple sclerosis as well as goiter, chorea and cardio vascular defects. One thinks of the big Swedes that live in this country. Probably the cardiovascular defects are associated with the tall stature of men from this locality."

It is of interest that as shown in the present series, tallness was present in a majority of patients' families.

That the nervous system of the Negro differs in many respects from that of the Caucasian is supported by much evidence. The Negro seems relatively immune to chorea (21). It is a well known fact that the Negro's nervous system suffers much less from syphilis than does that of the Caucasian. Fairbairn (22), for instance, says that in a discussion on neurosyphilis in the tropics all of the speakers stated that this condition is rare and very few cases were reported, although all of them had had extensive experience with work in the tropics. Zieman (23a) said that he had only seen two cases among West Indians. Kirschner (23b) saw two cases in 3800 native patients. Kelly (24) said that tabes dorsalis and general paralysis of the insane were infrequent and the few cases of the latter

which were seen generally occurred among those who did not perform hard manual labor. Cook (25) said that in the Protectorate very few cases of locomotor ataxia or dementia paralytica were to be seen and he could not recall seeing one case of general paralysis of the insane among the population. Nelson (26), Noronha (27), Pearce (28) and many others agreed that neurosyphilis is rare in the natives of the tropics. Lehmann (29) gave the percentage of tabes dorsalis in the Caucasian as 80 per cent and only 20 per cent in the Negro.

Paskind (30) from the results of his studies concluded that the Negro is less susceptible than the Caucasian to the central action of atropine.

Vint (31) found the brain of the Kenya native to weigh 10.6 per cent or 152 gm. less than the average weight given for the brain of the European. Miller (32) said that the nervous system of the Negro exhibits a lessened sensibility to pain and shock and that the pure black type is the safest surgical risk to be found in our hospitals, although the mulatto is a poorer surgical risk than either of the pure races.

Of interest is the rarity of ectodermal epithelial involvement in the Negro. The fragmentary evidence available seems to justify the conclusion that malignant tumors in the slave population were extremely rare corresponding in this respect to present day conditions in practically all parts of Africa.

Hoffman (33), in studying the statistics of the Metropolitan Life Insurance Company for the years 1911 to 1922, found that the rate for cancer of the skin was 2.1 per cent for Caucasian males and 0.7 per cent for colored males, the rate for the female Caucasian was 1.6 per cent and the Negro was 0.8 per cent. Cancer of the skin constituted only 1.4 per cent of the Negro deaths from cancer in the United States during 1923 to 1927. In the total American population in 1927 this proportion was 2.8 per cent. Thus there is a marked difference in favor of the Negro in cancer of the skin which is deserving of consideration. In Detroit for the year 1930 the Caucasian rate for cancer was 75.6 and the Negro 38.3 (34).

The relatively high incidence of arthritis in women who have uterine fibromyomas is no doubt of some importance. Since the etiology of the uterine fibromyomas and arthritis are both unknown, speculation is useless. The same may be said for hypertension. It will be noted that 105 (29%) of the 362 patients who had the blood pressure recorded had systolic readings ranging from 140 to 270 mm. Hg, and the average age of this group was 45 years. Approximately one third of the series, therefore, have either a mild or severe hypertension. Of course these patients are in the age level at which hypertension is apt to occur, but this does not detract from the fact that there is a sizable number who have this condition.



## SUMMARY

A series of 410 uterine fibromyomas associated with other clinical conditions is reported in Caucasian women. The average age in the series was 42 years.

Two hundred and sixty-eight (65%) had a hysterectomy. Sixty-seven (18%) had radium therapy. Two hundred and fifty-three (63%) had goiter. One hundred and twenty-nine (37%) were subject to migraine headaches. One hundred and sixteen (28%) had some form of arthritis, the majority of cases being classified as osteoarthritis or hypertrophic arthritis.

Sixty (22%) of the 268 hysterectomized cases had cholelithiasis.

Three hundred and fifteen (75%) had one or more members of the immediate family who were 72 inches or more in height.

One hundred and five (29%) of 362 patients whose blood pressure was recorded had systolic readings from 140 to 270 mm. Hg. The average age of this group was 45 years.

Attention was called to the fact that uterine fibromyomas are more common in Negro women. On the basis of a high incidence of adenomatous goiter in Caucasian women with fibromyomas, as shown in this series, Negro women should show a much greater incidence of goiter. Such is not the case and a racial singularity was invoked to explain the difference.

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# Effect of an Excess of Ingested Carbohydrate upon the Glycogen Content of Vaginal Epithelium

## [Vaginal Cell Glycogen]

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THAT GLYCOGEN is present in the epithelial cells of the vagina has been recognized for years, but factors responsible for quantitative changes in glycogen have not been investigated in detail. In the past such studies required a complicated staining technique. Since the introduction of the iodine vapor method by Mack (1) this obstacle has been overcome and future studies should be easier and may reveal valuable information concerning the physiology of the female generative tract.

The presence of glycogen in the vaginal cells of newborn infants and sexually mature women, with a decrease or complete absence during childhood and the postmenopausal period suggests that the estrogenic hormone plays a part in its deposition. This assumption is corroborated by the appearance of glycogen coincidental with the increase in cornification in the vagina of children undergoing estrogenic treatment for gonorrheal vulvovaginitis (2) and during substitutional therapy in menopausal women. The studies of McLaren (3) on postmenopausal women, however, show that the age limits within which glycogen has been assumed to be absent are too sharply drawn. He was able to demonstrate small amounts in all sections of the vaginal wall examined regardless of the time which had passed since cessation of menstrual periods.

Because our knowledge regarding factors responsible for glycogen mobilization in the vaginal mucosa is so meager this study was undertaken to provide information concerning the effects of an abnormally high carbohydrate diet upon the glycogen content of the vagina as shown by vaginal smears stained specifically for that substance.

### METHOD OF STUDY

A group of 14 postmenopausal women was selected

from the patients of the Ypsilanti State Hospital. The youngest subject was 64 years of age and the oldest 86. The selection was made from a larger potential group and these particular individuals were chosen because all demonstrated definite atrophic changes in the genitalia and none had any demonstrable physical or gynecological abnormality which might have influenced the results. All of the patients were ambulatory and on the general hospital diet.

Vaginal smears were taken twice weekly and stained for glycogen by the iodine vapor method. The glycogen content of the cells as demonstrated in this manner was compared at intervals with Best carmine stains on identical spreads. Shorr stains for cell type were made prior to and during treatment.

The glycogen smears were graded from + to + + + +, the gradation being primarily on the basis of the number of glycogen-containing cells. The smears were read in the following manner:

- +, only an occasional glycogen containing cell
- ++, less than one third of the cells contained glycogen
- +++, from one third to two thirds of the cells contained glycogen
- + + + +, more than two thirds of the cells contained glycogen

The Shorr stains were graded according to the degree of cornification of the cells. Those definitely unstimulated were read as atrophic. The various degrees of cornification were recorded as early, moderate, advanced or complete.

After an initial period of three weeks of observation without treatment the patients were divided arbitrarily into three groups. During the remainder of the study the 5 patients in Group I were given 200 gm of carbohydrate daily in excess of the general diet. After three weeks on the added glucose each was given 1 mg of diethylstilbestrol daily for 12 days. Those in Group II (5 patients) were given no added carbohydrate but took diethylstilbestrol in the same

manner and at the same time as those in *Group I*. The 4 patients in *Group III* were given 200 gm. of carbohydrate daily during the period of investigation but no estrogenic substance. The glucose was given in the form of clear hard candy and all of the subjects were kept under careful observation to insure their consuming the total amount of added glucose as well as the normal daily diet.

### RESULTS

*Glycogen content of the vaginal cells before treatment.* Glycogen was found in the smears of every patient

TABLE 1. PRETREATMENT VAGINAL SMEAR EXAMINATIONS

| Patient | Age, Years | Average Glycogen for 3 Weeks Before Treatment | Cell Type |
|---------|------------|---|-----------|
| 1       | 66         | ++  | Atrophic  |
| 7       | 79         | ++++  | Early     |
| 10      | 68         | ++++  | Early     |
| 13      | 64         | ++  | Atrophic  |
| 16      | 86         | ++++  | Moderate  |
| 2       | 80         | ++  | Atrophic  |
| 3       | 73         | ++  | Early     |
| 6       | 77         | ++  | Early     |
| 8       | 84         | ++++  | Atrophic  |
| 12      | 75         | ++++  | Early     |
| 4       | 67         | ++  | Early     |
| 5       | 70         | +   | Atrophic  |
| 11      | 73         | ++++  | Atrophic  |
| 15      | 71         | +   | Atrophic  |

despite the fact that all showed definite atrophic changes in the genitalia and all were at least 12 years postmenopausal. While in some instances the amount of glycogen was small the smears from several untreated patients were read consistently as +++ (table 1). During the initial 3-week period of study without treatment little change was noted in the glycogen content. A comparison of the glycogen content and cell type (table 1) shows that in almost every instance in which the smears were graded as atrophic there were only small amounts of glycogen while in those in which there was more cornification

the glycogen was deposited in a greater concentration. It is of interest that *patient 16* who was 86 years of age consistently showed a moderately advanced stage of cornification of the vaginal mucosa and glycogen in about half of the smeared cells.

*Glycogen response to the administration of carbohydrate.* Nine patients (*Group I* and *III*) were given extra carbohydrate. In table 2 is tabulated the glycogen content of the vaginal cells during the 3-week period of carbohydrate administration as compared with the pretreatment smears. No increase in glycogen was noted except in *patient 15* in whom there was a change from + to ++ during the first week of glucose administration. The actual increase in the amount of the substance as observed in the smears, however, was very slight. No change in the cell type could be detected in the stained smears.

*Glycogen response to the administration of diethylstilbestrol.* In table 3 is shown a comparison of the response of the vaginal cells in *Groups I* and *II* to stimulation with diethylstilbestrol. In both groups there was a definite increase in glycogen content apparent within one week. The increase was noted as a greater concentration in the individual cells and an increase in the number of glycogen-containing cells. No differences in rapidity of response or in total quantity of glycogen deposited could be detected between the two groups although the subjects in *Group I* continued to take the added glucose.

The response as evaluated by increase in cornification of the cells likewise was not altered by the previous administration of carbohydrate. In both groups it was noted that an increase in the amount of glycogen could be observed before there was much alteration in cell type and also that a change to an advanced stage of cornification did not necessarily accompany a heavy glycogen infiltration (table 3, *patients 1, 13, 2*).

Three patients (*1, 10, 16*) had withdrawal bleeding following the administration of diethylstilbestrol. The flow was scant in amount, began two days after the drug was stopped and lasted two days.

TABLE 2. GLYCOGEN CONTENT DURING CARBOHYDRATE ADMINISTRATION

| Patient | Average Pretreatment Glycogen Content | Glycogen Content During 3 Weeks of Treatment with 200 Grams of Excess Carbohydrate Daily |        |        |        |        |        |        |
|---------|---------------------------------------|--|--------|--------|--------|--------|--------|--------|
|         |                                       | Week 1   | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 |
| 1       | ++                                    | ++   | ++     | ++     | ++     | ++     | ++     | ++     |
| 7       | ++++                                  | ++++   | ++     | ++     | ++     | ++     | ++     | ++     |
| 10      | ++++                                  | ++   | ++++   | ++++   | ++     | ++     | ++     | ++     |
| 13      | ++                                    | ++   | ++     | ++     | ++     | ++     | ++     | ++     |
| 16      | ++++                                  | ++++   | ++     | ++     | ++     | ++     | ++     | ++     |
| 4       | ++                                    | ++   | ++     | ++     | ++     | ++     | ++     | ++     |
| 5       | +                                     | ++   | +      | ++     | ++     | ++     | ++     | ++     |
| 11      | ++++                                  | ++++   | ++     | ++     | ++     | ++     | ++     | ++     |
| 15      | +                                     | +  | ++     | ++     | ++     | ++     | ++     | ++     |

TABLE 3 GLYCOGEN CONTENT AND CELL TYPE DURING DIETHYLSTILBESTROL THERAPY

| Patient  | No Diethylstilbestrol |           | Diethylstilbestrol, 1 milligram Daily |           |                               |           |                                |           |
|----------|-----------------------|-----------|---------------------------------------|-----------|-------------------------------|-----------|--------------------------------|-----------|
|          |                       |           | 4 Days<br>Total, 4 milligrams         |           | 8 Days<br>Total, 8 milligrams |           | 12 Days<br>Total 12 milligrams |           |
|          | Glycogen              | Cell type | Glycogen                              | Cell type | Glycogen                      | Cell type | Glycogen                       | Cell type |
| 1        | ++                    | Atrophic  | ++                                    | Atrophic  | ++                            | Atrophic  | +++                            | Early     |
| 7        | +++                   | Atrophic  | ++                                    | Early     | ++++                          | Moderate  | ++++                           | Advanced  |
| 10       | +++                   | Early     | +++                                   | Early     | +++                           | Moderate  | ++++                           | Advanced  |
| 13       | ++-+++                | Early     | +++                                   | Early     | +++                           | Early     | ++++                           | Early     |
| 16       | +++                   | Moderate  | +++                                   | Moderate  | ++++                          | Advanced  | ++++                           | Advanced  |
| Group II |                       |           |                                       |           |                               |           |                                |           |
| 2        | ++                    | Early     | ++                                    | Early     | ++                            | Early     | ++++                           | Early     |
| 3        | ++                    | Early     | +                                     | Moderate  | ++                            | Advanced  | +++                            | Advanced  |
| 6        | ++                    | Early     | ++                                    | Moderate  | ++                            | Moderate  | ++++                           | Advanced  |
| 8        | +++--                 | Atrophic  | +++                                   | Early     | ++++                          | Advanced  | ++++                           | Advanced  |
| 12       | +++                   | Early     | ++                                    | Early     | ++++                          | Moderate  | ++++                           | Moderate  |

## SUMMARY

The ingestion of glucose by the normal human being results in a temporary rise in blood sugar which is followed by an increase in liver and muscle glycogen and possible glycosuria (4). This occurs regardless of the age of the individual and is the result of the protective body mechanism by which the blood sugar level is stabilized.

Variations in glycogen content of epithelial cells of the vagina appear to reflect the level of the estrogenic hormone in the body rather than the amount of carbohydrate available to the cells. If this supposition is correct the vaginal cells during childhood and old age, when the estrin production is at a minimum, should be devoid of glycogen. This study of the glycogen content as seen in vaginal smears from a group of women well past the menopause shows that small amounts of glycogen are present in all cases regardless of the age and degree of atrophic change in the tissues. This may be interpreted as indicating the presence of small amounts of estrin or else that estrin is not entirely responsible for the control of glycogen deposition in the vaginal epithelium.

An increase in the carbohydrate intake to a point well above average produced no noticeable change in the concentration of glycogen. A comparison of response to the administration of diethylstilbestrol in patients being given extra carbohydrate and in those on a normal diet revealed no change either in the rapidity with which the glycogen was laid down in the cells or in the total amount deposited during the test period.

The accuracy of the iodine vapor method for staining glycogen was checked by a comparison with identical slides stained by the Best carmine procedure. The amount of the material stained by the two methods was quantitatively comparable.

## CONCLUSIONS

- 1 The results of a study of glycogen mobilization in the vaginal mucosa of postmenopausal women are presented here.
- 2 Glycogen was demonstrated in the vaginal smear of every patient regardless of her age.
- 3 The administration of excessive amounts of carbohydrate resulted in no change in the glycogen content of the vaginal cells.
- 4 Diethylstilbestrol, 1 mg daily for 12 days, produced a definite increase in the amount of glycogen in all cases. No difference in response to the estrogenic substance was noted in patients on an abnormally high carbohydrate diet as compared with those whose sugar intake was normal.
- 5 The iodine vapor method of staining for glycogen is simple, inexpensive, and accurate.

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# Dermovascular Changes during the Menstrual Cycle: Failure to Find a Cyclic Variation in Contractile or Dilating Capacity of Capillaries of the Skin<sup>1</sup>

## [[Cyclic Vascular Changes]]

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AN EFFORT WAS MADE to learn if a cyclic variation in the condition of the smallest blood vessels of the skin occurs from one menstrual period to the next. A number of correlations between somatic, functional states and menstruation have been claimed, a few demonstrated and others denied (1, 2, 3). By utilizing a new method for evaluating the threshold of contractile excitability of the smallest blood vessels of human skin in response to graded mechanical stimulation (4, 5) it was possible to learn if 'premenstrual tension' or premenstrual increase in body weight was correlated with a change in the functional capabilities of the smallest cutaneous blood vessels. In addition, data were obtained on the vasodilating capacity of these blood vessels by a method likewise recently developed. This second method grades the response of reactive hyperemia to a controlled pressure device for producing local circulatory stasis (5, 6). Briefly, the data from both series of tests failed to show any consistent variation in dermovascular responsiveness (contractility or vasodilating capacity) during the menstrual cycle.

Six women medical students and one research assistant, all in good health, and between 22 and 28 years of age were studied during a total of twenty-four menstrual cycles. The length of the cycles, and the number during which any individual was examined, are shown in figure 1. Strength-duration curves of capillary contractility were obtained 66 times in all. Data on reactive hyperemia were obtained more than one hundred and fifty times. The results may be summarized as follows.

*Tests for vasodilating capacity (reactive hyperemia).* The data from these women were obtained on the skin of the forearm from November, 1940 to June, 1941. At the same time, data were obtained on a group of 100 men of about equal ages. The two sets of data were wholly super-imposable, and showed a characteristic seasonal variation which has been reported in detail elsewhere (6). There was never any evidence that the threshold for reactive hyperemia varied with the menstrual cycle, even when observations were made a day, or a few hours before the onset of menstruation, nor was there any characteristic change during the period of blood flow, or near the middle of any of the cycles studied. Observations were made, for the most part, at weekly intervals, but at times which were thought might have been crucial in the menstrual cycle, observations were frequently made twice or three times weekly.

*Tests for capillary contractility.* Fewer data have been obtained with respect to these data than with the former. Sixty-six curves were obtained on the inner aspect of the forearm; in at least six menstrual cycles, curves of dermovascular excitability were obtained four to seven times. With respect to the rest, the days of the cycle on which the data were obtained was carefully kept; a written record of the length of each cycle was also kept.

In order to bring the data together, the days of a cycle were expressed as a percentage of the whole cycle. By the device shown in figure 1, the separate coefficients of excitability [reciprocal of the products of the rheobase<sup>2</sup> and the chronaxie, in a strength-duration curve (7)], are correlated with the relative times in the several cycles when the curves were obtained. Clearly, there is no clean-cut correlation between the contractile excitability of the blood vessels and the menstrual cycle. That it would have been

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# Dermovascular Actions of Certain Steroid Hormones in Castrate, Eunuchoid and Normal Men<sup>1</sup>

## [Dermo-vascular Change]

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AMONG THE EFFECTS on somatic tissues of estrogenic and androgenic hormones, those involving the cutaneous blood vessels are particularly noteworthy. The evidence for this statement is both experimental and clinical. Clinically, both types of hormones have served to provide relief from flushes resulting from gonadal insufficiency. In this regard the actions are in part indirect, involving the central nervous system, and in part directly upon the blood vessels themselves (1, 2, 3).

From the experimental standpoint, androgenic substances have been shown to alter both the amount of blood in the cutaneous vessels, and the ratio of oxygenated to reduced hemoglobin (4). In general, the quantity of oxyhemoglobin increases relative to the amount of reduced hemoglobin, following injection of testosterone propionate into castrate and eunuchoid men. As for estrogens, these have been found to dilate the smallest blood vessels of the rabbit's ear (5) and to increase the amount of acetylcholine, a potent vasodilator, in certain tissues such as the uterus of the rabbit (1, 6), and the nasal mucosa of rabbits and cats (7).

The above mentioned effects would seem to be, at least in part, reflections of changes in the condition of the smallest blood vessels. The experiments reported

in this paper are attempts to determine directly the character and extent of changes in the cutaneous blood vessels following administration of certain steroids to castrate, eunuchoid, and normal men.

### METHODS AND PROCEDURES

The present studies are based primarily upon two new methods for testing the sensitivity of the smallest cutaneous blood vessels to graded stimulation. One method, already employed in measuring the irritability (vasoconstriction) of blood vessels in normal subjects (8), tests the sensitivity of cutaneous blood vessels to various intensities of mechanical stimulation. The intensity of stimulation can be accurately controlled and varied at will with regard to either the rate or the force of application.

The second method rests upon a quantitative measure of the time required for a period of local ischemia to elicit a given degree of reactive hyperemia. This response is the result of the production within the tissues of vasodilating substances. The normal range of individual and seasonal values (9) offers a basis for comparison with the vascular actions of the steroid hormones. Details of the routine in these and in the other tests employed are as follows.

Each subject came to the laboratory in the early afternoon. After a period of relative quiet, observations were begun. First, the threshold time for production of a given degree of reactive hyperemia was measured.

This was followed by determination of the intensity-duration curve for the excitation of capillary contractility. This consists of measuring on the inner aspect of the forearm the minimal weight necessary at any given rate of application to evoke a light line of erythema along the

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path followed by the automatically-driven contact point. The line of erythema appears in the center of an area of pallor (vasoconstriction). This threshold response, which may be determined to within 20 gm or less in a total of from 200 to 1,000 gm, comprises the first two steps of the 'triple response' (10).

The next measure was of the effect of circulatory stasis on the above described threshold to mechanical stroking. The procedure was designed to gauge the sensitivity of the contractile elements of the blood vessels to deprivation of oxygen, this method has been accorded extended study in an earlier paper on other subjects (8).

The third measurement was of changes in the skin temperature of the forehead, hands and lower leg. These were made with the patient in recumbent and standing positions in order to gauge vasomotor adjustments to postural changes (cf. 11).

On the following morning the subject returned to the laboratory for repetition of the determinations of the previous day. In addition, examination was made of the effect of iontophoretic passage into the skin of definite amounts of eserine sulfate. A fresh solution was prepared in a concentration of 0.1 mg per cc. of distilled water and applied on a saturated cotton pad around a brass electrode (diameter of 1.9 cm) which served as the anode. The current was 22.5 volts at 1 milliamperes. The passage of the current continued 1 minute and in a few instances, for either 2 or 4 minutes. The extent and development of the pattern of erythema at intervals of five minutes denoted the sensitivity of the cutaneous blood vessels to the dilating action of eserine. The procedure was employed in an attempt to ascertain whether or not the hormones rendered the blood vessels more susceptible to a drug which sensitizes the tissue to the action of acetylcholine.

Tests of capillary fragility by the suction method were also made according to the technique of Brewer (12).

Immediately after completion of these procedures, the subject was prepared for injection of hormone. He was seated comfortably with one finger in a plethysmograph sealed with care to allow return of venous blood from the digit. A 30 gauge thermocouple junction of iron and constantan leading to a Leeds and Northrop (Micromax) recording potentiometer, was used to obtain a continuous record of the nail bed temperature. When the droplet in the plethysmograph oscillated about a constant level with each heart beat, the injection of hormone was made intramuscularly in the contralateral upper arm. Room temperature and relative humidity were noted at intervals. The effects of the injection upon finger volume and skin temperature were thus observed for from one half to a full hour. The data were plotted together on single coordinate paper. Upon completion of this procedure the tests employed prior to administration of hormone were repeated with notation as to the respective times since the injection. In some experiments, the more significant tests were repeated several times such as at 3 to 4, and 5 to 6 hours after the injection.

On the third day control readings were taken, the second injection given and the routine tests again repeated.

In contrast to the studies of castrate and eunuchoid men, the normal subjects were tested only on separate, rather than consecutive days.

The subjects used in this study included two castrate and two eunuchoid men who had been employed in an earlier spectrophotometric study of cutaneous blood vessels and their response to androgens (4). Other subjects included a normal man of 37 years, who was observed repeatedly in investigations of the effects of estrogen (13) and another normal man 26 years of age.

Tests were made before and after administrations of various hormones: a), testosterone propionate (20 mg per injection) in 13 instances, twice in normal subjects, twice in eunuchoids and nine times in castrates, b), desoxycorticosterone acetate (5 mg per injection) once in a normal subject and twice in two castrates, c), progesterone (5 mg. per injection) once each in normal and castrate subjects, d), estradiol monopropionate (2.5 mg per injection) once in a normal subject (who had been observed upon receiving six such injections in the earlier study (13)), and twice in two castrates. One cc. of peanut oil was used as the vehicle for all of the hormones. Control experiments included injections of this solvent alone twice into a normal subject and three times into two castrates. The type of material injected, i.e., hormone or blank injection was not disclosed to the subjects. Studies extended from December, 1940 to June, 1941.

## RESULTS

### *Findings in Untreated Castrate and Eunuchoid Men That Did Not Differ Notably from Those in Normal Men*

The capacity of the blood vessels to dilate and contract, as tested by local ischemia, was not unlike that in a large group of normal subjects. The seasonal trend (cf. 9) and ease with which reactive hyperemia is elicitable was in all four cases within the standard deviation of a group of 100 normal individuals.

Susceptibility of the blood vessels to graded mechanical stimulation (white reaction) was within the normal range, the average of the Lassalle coefficient in castrates being  $0.85 \times 10^{-4}$  and  $0.82 \times 10^{-4}$  respectively (see below for a description of the Lassalle coefficient of excitability). In the earlier study of 38 normal men, the mean coefficient was  $0.53 \times 10^{-4}$  with a standard error of the mean of  $\pm 0.08$ . Thus the data for the two castrates fall outside the significant mean value for normal subjects, but in view of the paucity of data and the fact that they are obtained from only two subjects, the conclusion is not warranted that the smallest cutaneous vessels of male castrates are more excitable than those of normal individuals.

In one respect, however, the susceptibility of the

\* The testosterone propionate (Perandren), desoxycorticosterone acetate (Perccorten) and progesterone (Lutoecylin) were furnished by the Ciba Pharmaceutical Products, Inc., Summit, N. J.



blood vessels to stimulation differed in castrate subjects from those in normal men. Their variability in reaction and 'spontaneous' instability are much greater than have been observed in any normal subject. Thus, in the normal man who has been studied most extensively, the coefficient of excitability has shown about a tenfold variation over a period of nine months, whereas the castrates have shown as much as a fifty-fold variation, within the space of three days. This variability could not be correlated with any particular event or condition.

The eunuchoid subjects had Lassalle coefficients of  $0.19 \times 10^{-4}$  and  $0.29 \times 10^{-4}$  respectively, and so ex-

hibited lesser excitability of the blood vessels to mechanical stimulation than did the castrate men. In spectrophotometric studies (4) various values in eunuchoid men differed from those in castrate subjects. The limited character of the data, since it involves only a few men, allows only the suggestion that these differences between eunuchoid and castrate subjects are real.

#### *Phenomena Not Affected by the Hormones Under the Conditions Employed*

Other of the tests gave results that were consistently negative or were unaffected in any consistent

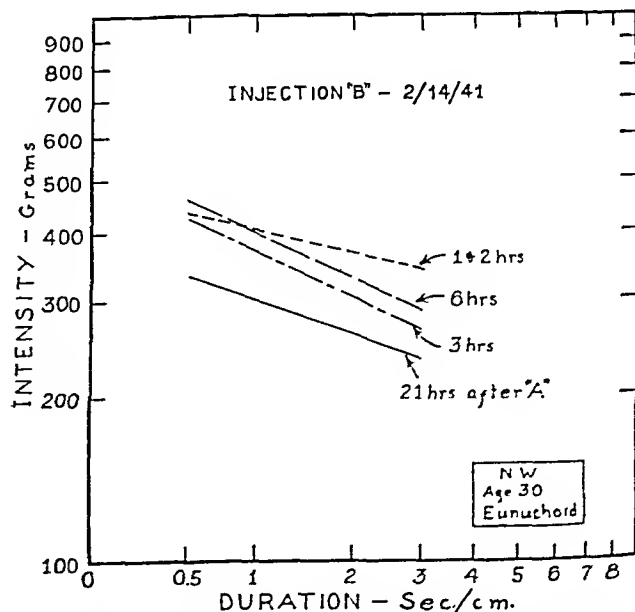
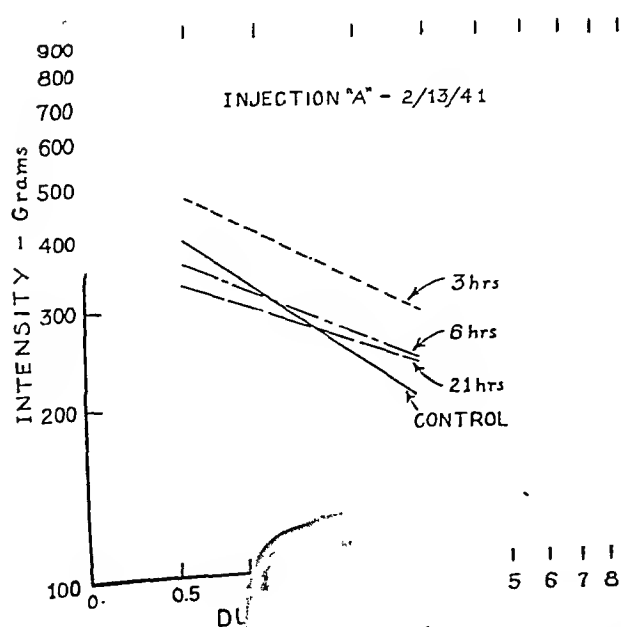
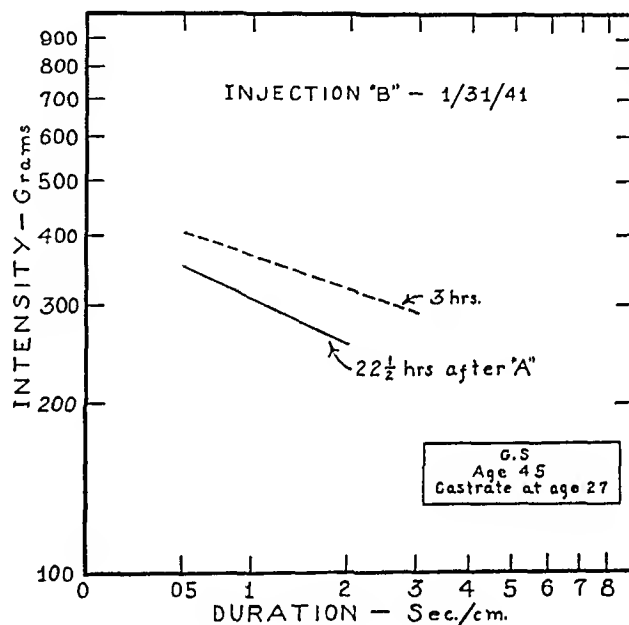
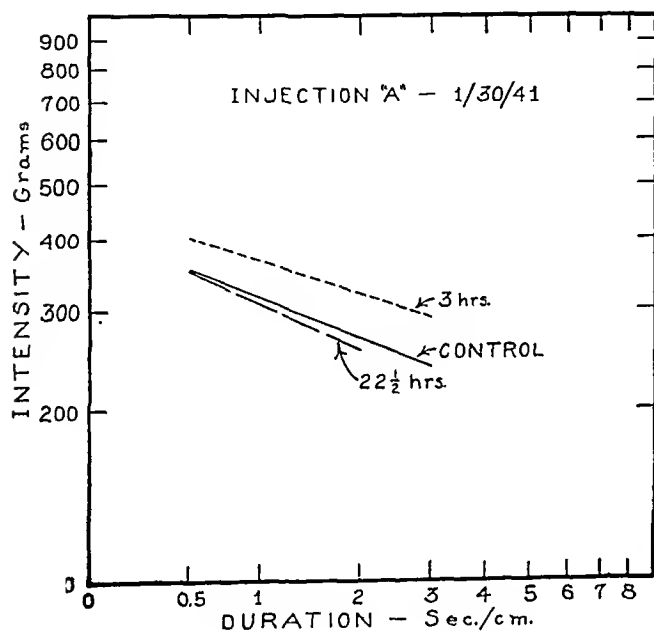


Fig. 1. CAPILLARY  
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LEVELS IN RESPONSE TO GRADED MECHANICAL STIMULATION. Plotted on logarithm-log<sub>2</sub> injection of testosterone propionate more weight is required to evoke a threshold finished. The upper set of curves are of the effects in a castrate man on 2 different

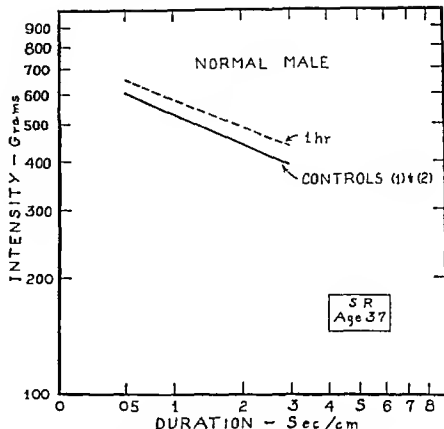
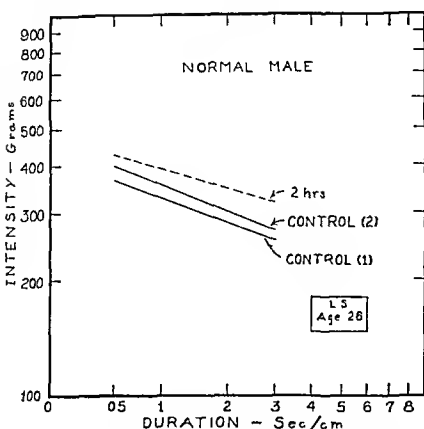


Fig. 2 TESTOSTERONE PROPIONATE CAUSES A DECREASE IN EXCITABILITY OF BLOOD VESSELS IN NORMAL SUBJECTS. This can be compared with figure 1 of castrate and eunuchoid subjects

manner by injected hormones. These included the adjustment of skin temperature to postural change, the response of the cutaneous blood vessels to ischemia (reactive hyperemia test), the sensitivity to eserine, and the fragility of the capillaries. Thus it is clear that arteriolar tone and its adjustment to change in position of the body is unaffected, at least within the first few hours, by any of the hormones used. Similarly, there is no altered susceptibility of the smallest cutaneous blood vessels to vasodilating substances, either as produced autogenously from local ischemia or as afforded in the introduction of eserine by iontophoresis.

#### Changes Induced or Influenced by the Hormones as Employed

**Contractility of capillaries.** The contractile response of cutaneous vessels upon graded mechanical stimulation is influenced by certain of the steroid hormones. Testosterone propionate raises the threshold of contractile response to mechanical stimulation, not only in castrate and eunuchoid but also in normal men. Exemplary changes are shown in figures 1 and 2 in which the logarithm-logarithm plotting of the intensity-duration curves are given prior to each injection (marked "control") and at selected times after administration of the hormone. Vertical increases in the position of the curves after injection of the subjects show the minimal additional weight necessary at each speed of application in order to elicit a threshold response.

The coefficient of excitability (Lassalle coefficient =  $\frac{I}{\text{rheobase}^2 \times \text{chronaxie}}$ ) shows a similar relationship in the direction of decreased excitability. In figure 3

and in subsequent graphs in which this value is indicated, the coefficient has been calculated, and any change in response after the injection is estimated in terms of percentage of deviation from the control value of the coefficient of excitability (8).

In general, these and other data show that during the first four hours following injection of testosterone propionate, there is a decrease in sensitivity (an increased threshold) for about four hours, but that by the sixth hour the excitability has returned to normal or greater than normal values, and so persists for as long as the measurements were continued (about 22 hours after injection).

As a point of correlation it is of interest to note in spectrophotometric evaluation of cutaneous vascular changes in castrate and eunuchoid subjects, that beginning within one hour after injection of testosterone propionate, there is an increase in the amount of oxygenated hemoglobin in the dermal vessels. "The action of male hormone began within one hour after injection, reaching a maximum effect in 2 to 3 hours" (4).

With injections of peanut oil alone, no regular change was observed in the excitability of the smallest blood vessels. In two tests of a normal subject, the oil was without measurable effect (fig. 4). In castrates some of the readings gave essentially control values, but there were instances, in keeping with the general observation of variable dermvascular irritability in these subjects, when there was considerable deviation from the pre-injection level, in the direction of increased excitability of the blood vessels (fig. 3). This erratic variability is in contrast to the consistent elevation of threshold (decrease in excitability)

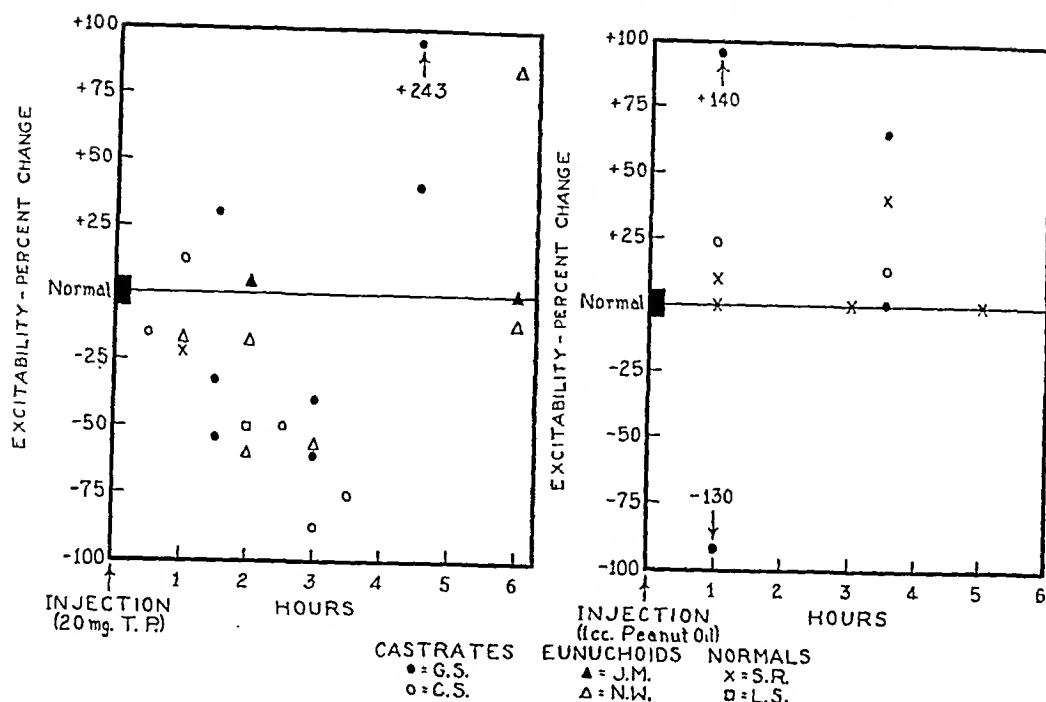


Fig. 3. COMPARISON OF EFFECTS IN THE SAME INDIVIDUALS OF TESTOSTERONE PROPIONATE (left chart) AND OF PEANUT OIL (right chart) ON THE EXCITABILITY OF DERMAL BLOOD VESSELS IN NORMAL, EUNUCHOID AND CASTRATE MEN. In the second chart, coefficients of excitability, calculated from the data of the intensity-duration curve observed in each man (see text), are compared in terms of percentage deviation from the control coefficient of excitability, which is the value observed prior to treatment with hormone.

observed following administration of testosterone (fig. 1, 2), and to the opposite effect of estradiol propionate, as described below.

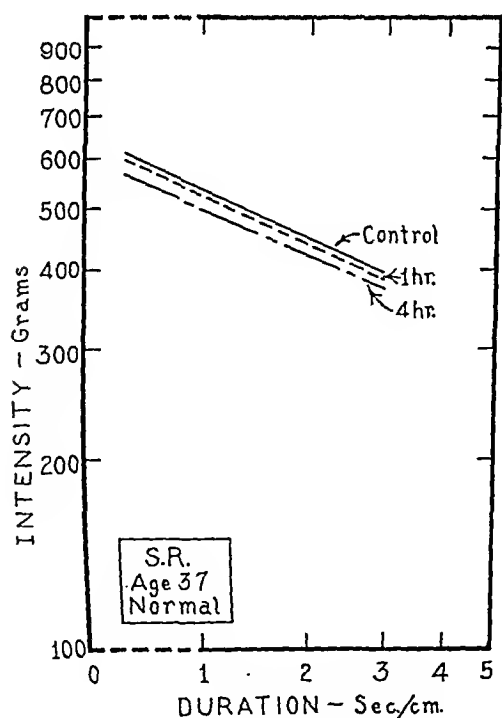


Fig. 4. EFFECT OF INJECTIONS OF PEANUT OIL. These exerted little influence on the intensity-duration curve of blood-vessel excitability in a normal man. In figure 3 is shown the variability in response of castrate men to mechanical stimuli, a variability not pronounced in the normal men under study.

The effect of the estradiol propionate is shown in figure 5. Whereas its influence as revealed in the logarithm-logarithm plotting was somewhat variable, the effect of the hormone as evaluated by the coefficient of excitability was consistent, namely an increased sensitivity of the blood vessels even in the normal subject whose vessels were unaffected by the injection of oil alone.<sup>4</sup>

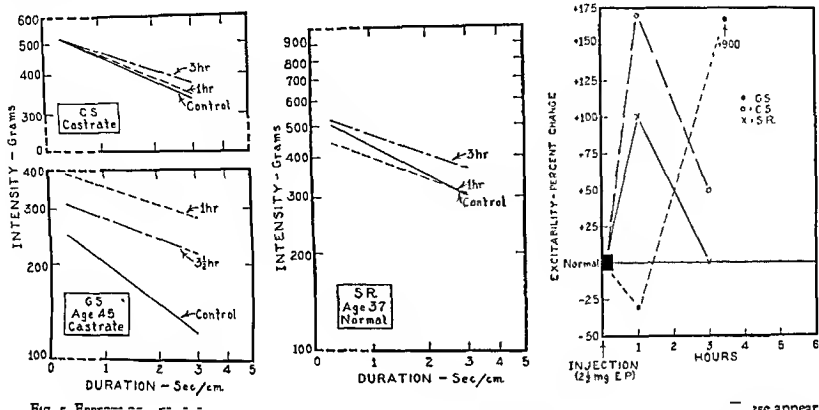
With desoxycorticosterone acetate, however, no regular variation is seen in either manner of analysis of the data. This is shown in figure 6 in which the intensity-duration curve in C.S. was elevated markedly after one hour, whereas in G.S. and S.R. they were raised only slightly and the coefficients of excitability were even decreased at the end of one hour.

The effect of progesterone, in the two cases in which it was used, was quite similar in both normal

<sup>4</sup> The apparent paradox of little, or no change, in the effect of estrogen when the data are plotted on the double logarithm paper but of regular change in the coefficient of excitability, lies in the fact that the coordinate plotting focuses attention upon the intensity parameter of the strength-duration curve through the region of inflection whereas the Lassalle coefficient encompasses the intensity parameter (rheobase) at one extreme of the curve and the time parameter at the other (chronaxie). Thus, the rheobase may become elevated, and so the intensity elevated in the logarithm-logarithm plotting, and the chronaxie shortened, as in the case with estrogens. In such a case, the coefficient may change in one direction and the graph show no change, or even an opposite one. Since both methods of treatment are wholly empirical (8) one feels doubly reassured when both vary in the same direction, as with testosterone propionate, although the effect of a procedure probably may be estimated when (as with estrogen) the findings with one method of evaluation are consistent, and not wholly offset or contravened by the other.

and castrate men. Within the first hour the curves of threshold responsiveness were elevated and the coefficient of excitability was lower (fig. 7). By the fourth hour the values of the coefficient were in the

fied compound); estradiol propionate apparently served to increase the excitability of the vessels; desoxycorticosterone acetate to be without a reg-



the control curve occupied the lowest position ever obtained on any subject, as seen in comparison with control curves on the same subject at other times (fig. 1, 6). A footnote is appended to the text concerning fluctuations in blood vessel excitability in castrate subjects.

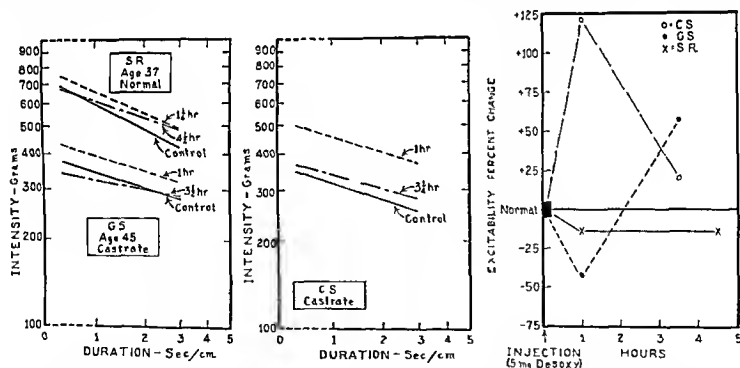


Fig. 6 EFFECT OF ADMINISTRATION OF DESOXYCORTICOSTERONE ACETATE TO ONE NORMAL AND TWO CASTRATE MEN. The substance exerted no regular influence on the threshold (left and center charts of intensity-duration curves in logarithm-logarithm plotting) or coefficient (right chart) of excitability.

reverse direction, indicating increased sensitivity of the blood vessels to mechanical stimulation.

All in all, therefore, testosterone propionate served to diminish capillary excitability during the first four hours; progesterone to diminish the sensitivity, but more transiently (perhaps related to the use of an unesteri-

ular or well-defined action in either direction.

**Susceptibility of blood vessels to ischemia.** The sensitivity of the dermal blood vessels to ischemia was not observed to change in the two normal subjects with any of the hormones used, but underwent change in men with testicular insufficiency upon use of 3 of the steroid substances employed. In castrate

and eunuchoid subjects the threshold to mechanical stimulation upon circulatory stasis was altered as follows. In 6 of 9 tests in castrates and 2 of 4 tests in eunuchoid subjects, the threshold was raised, that is, the vessels were less excitable by testosterone propionate; with desoxycorticosterone acetate it was elevated 2 or 3 times in castrate subjects; with progesterone it was raised in a single test in a castrate

the dermovascular actions of estradiol propionate and testosterone propionate, although it must be recognized that the latter compound was employed in quantities eight times greater by weight than that of the estradiol propionate. Use of these larger quantities is in keeping with the employment of clinically effective doses. In the present observations the increase in finger volume following administration of

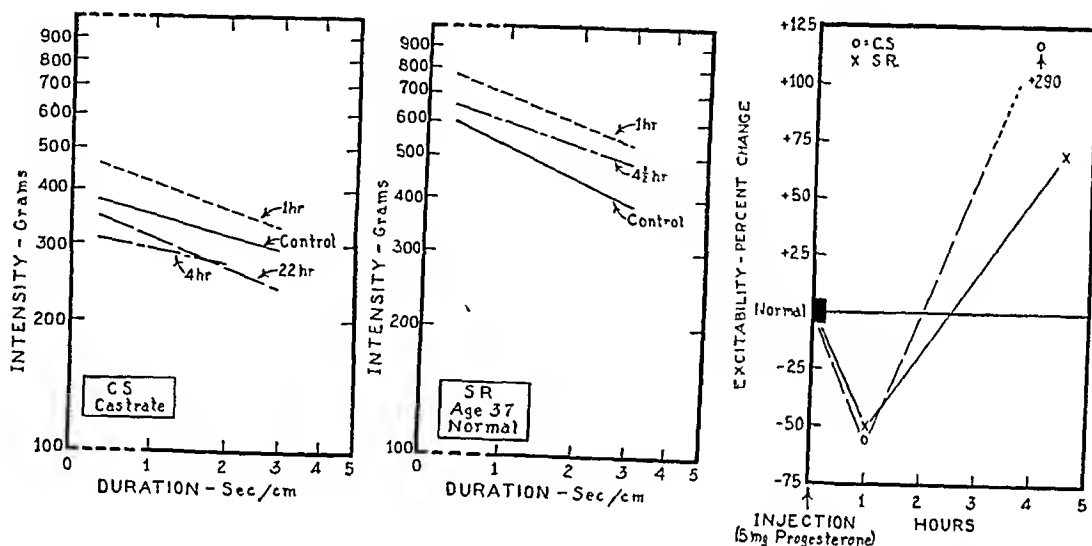


Fig 7 ADMINISTRATION OF PROGESTERONE TO A NORMAL AND TO A CASTRATE MAN This was followed within an hour by an increased threshold of excitability (left and center charts of intensity-duration curves with logarithm-logarithm plotting) and lower coefficients of excitability (right chart)

man. Estrogen had no measurable effect on blood vessel excitability following stasis in normal or hypogonadal individuals. These results signify, therefore, that the responses of the smallest blood vessels of the skin in castrate and eunuchoid subjects are affected by these hormones, testosterone propionate in particular rendering the vessels less susceptible to oxygen-lack, resulting from circulatory stasis.

**Finger volume.** Testosterone propionate gave rise in several instances to significant increases in the finger volume of castrate men. This was observed in 3 of 4 tests, with changes in volume ranging from 0.72 to 4.9 per cent. These values compare in magnitude with those which follow injections of estrogens in normal men and in menopausal women.

No effect on finger volume was observed with the use of estradiol propionate, progesterone or desoxycorticosterone acetate; this in marked contrast to the appreciable increase in volume induced by estrogen in normal men (13) and menopausal women (2). Estradiol propionate as well as desoxycorticosterone acetate, progesterone, and peanut oil were without effect in all tests in eunuchoid and castrate subjects. The oil vehicle either with or without testosterone propionate exerted no appreciable effect in the normal subject.

There appear to be important differences between

testosterone propionate was accompanied in some instances by an appreciable elevation of skin temperature. This is the result of an increase in the rate of blood flow through the skin, and is in part presumably a reflection of relaxed tone in the dermal vessels, probably of the arterioles. With estrogen, however, the cases observed in a previous study (13) had an increase in finger volume unaccompanied by a change of skin temperature. When such a response to estrogen occurs, therefore, it may be the result of increase in fluid outside of the blood vessels (14) or of dilatation of the smallest vessels beyond the terminal arterioles. This latter possibility is supported by direct observation of the dilating effect of estrogen upon the blood vessels of the ear to castrated rabbits (5). Unpublished data (Edwards and co-workers) obtained by spectrophotometric study show, moreover, that injection of estradiol propionate (2.5 mg) into two castrate men failed to give the large increase in the quantity of hemoglobin and shift to oxyhemoglobin observed upon injection of these same men with testosterone propionate (20 mg.). Thus there appear to be fundamentally different vascular actions of androgens and estrogens, differences that are demonstrable with respect to their sites of action, the nature of gonadal insufficiency at the time of injection, and the effects on the susceptibility of the

smallest blood vessels to trauma and circulatory stasis

# DISCUSSION

Little need be said regarding the results of this study, recapitulated in table 1. Of all the data, there is one prominent feature which should be of most general interest. It pertains to three related facts: a) In hypogonadal men, especially castrates, great instability of the cutaneous vessels is encountered. This is so clinically, and we have found this to be associ-

In conclusion, one further correlation may be made. Only estradiol of the steroids tested, failed to affect the excitability of the smallest blood vessels in the skin during local anoxia. One naturally asks how it differs from the others, stereochemically, or conversely, what the other three steroids have in common, in this respect. One common feature which these three molecules with similar actions possess is that they are alpha, beta unsaturated ketones, with the carbonyl group in position 3 and the alpha carbon at  $\Delta^4$ . The fact that testosterone was so much more

TABLE 1 TESTS OF DERMOVASCULAR ACTIONS OF STEROID HORMONES

| Hormone Used                 | Vasodilation of Smallest Vessels |                          | Vasoconstriction of Vessels            |  | Fragility of Capillaries, (suction) | Finger Volume Change After Injection (plethysmograph) | Susceptibility of Capillaries to Lack of Oxygen | Types of Subjects               |
|------------------------------|----------------------------------|--------------------------|--|--|-------------------------------------|---|---|---------------------------------|
|                              | Reactive hyperemia               | Eserine by iontophoresis | Excitability, (capillary constriction) | Arteriolar adjustments, (with change in posture) |                                     |   |   |                                 |
| Testosterone propionate      | o<br>o<br>o                      | o<br>o<br>o              | —<br>—<br>—                            | o<br>o<br>o                                      | o<br>o<br>o                         | +<br><br>o  | —<br>—<br>o                                     | Castrate<br>Eunuchoid<br>Normal |
| Progesterone                 | o<br>o                           | o<br>o                   | —<br>—                                 | o<br>o   | o<br>o                              | o<br>o  | —<br>o  | Castrate<br>Normal              |
| Estradiol propionate         | o<br>o                           | o<br>o                   | +<br>+                                 | o<br>o   | o<br>o                              | o<br>+  | o<br>o  | Castrate<br>Normal              |
| Desoxycorticosterone acetate | o<br>o                           | o<br>o                   | o<br>o                                 | o<br>o   | o<br>o                              | +<br>o  | —<br>o  | Castrate<br>Normal              |
| Peanut oil                   | o<br>o                           | o<br>o                   | o—+<br>o                               | o<br>o   | o<br>o                              | o<br>o  | o<br>o  | Castrate<br>Normal              |

ated with transient and extensive increases in excitability to direct mechanical stimulation b) A result of androgen administration is to increase the amount of oxyhemoglobin in the cutaneous blood vessels of hypogonadal men, especially castrates c) And the smallest blood vessels in the skin of hypogonadal men are less excitable to mechanical stimuli during local anoxia after injection of androgen than before, this was the case with three of the four steroids employed (all but estradiol). The inferences to be derived from this association of facts are several. They suggest that the primary deficiency in hypogonadal men stems from the fact that the smallest blood vessels are denied an optimal complement of oxygen, in the form of oxyhemoglobin, they manifest this lack by vasomotor instability and ready susceptibility to further oxygen lack. By analogy, therefore, the dermovascular action of androgens (and related substances) may mean that alleviation of vasomotor instability in hypogonadal males depends largely, if not primarily, upon augmentation of the available oxygen supply. Estrogen lacks this particular pharmacodynamic action which androgens clearly possess in hypogonadal men.

effective than the other substances in the present experiments may best be explained on the grounds that it was used in much higher dosage than were progesterone and desoxycorticosterone acetate.

The intriguing question remains for future investigation, therefore, as to why this particular chemical moiety in ring I of a steroid substance evokes this specifically demonstrable action.

## SUMMARY

Upon two castrates, two eunuchoid and two normal men repeated measurements were made of a number of cutaneous vascular and vasomotor adjustments following single injections of certain steroid hormones, and of the peanut oil vehicle alone. The hormones employed were testosterone propionate, estradiol propionate, progesterone, and desoxycorticosterone acetate.

Some of the tests reflected no difference between normal and hypogonadal men. These tests included a), the contractile response of the blood vessels upon graded chemical stimulation of the integument, b), the vasomotor adjustment of dermal blood vessels to postural changes, c), the ease with which reactive

hyperemia was induced by local ischemia; d), the effects produced by eserine, as introduced by iontophoresis; and e), capillary fragility. In all of these respects the responses of dermal blood vessels of castrates and eunuchoids did not definitely exceed normal limits.

The excitability of the cutaneous blood vessels as measured by graded mechanical stimulation was far more variable in castrate than in normal men. The variations were characterized by the suddenness of their appearance and by their extensiveness.

Two of the hormones rendered blood vessels less excitable in all subjects tested. Testosterone propionate had the most marked effect which reached a maximum about the fourth hour following the injection. Progesterone had a similar action, but less marked and more transient. Desoxycorticosterone acetate exerted no consistent influence. The excitability of the blood vessels in all subjects was increased slightly and in a transitory fashion by estradiol propionate. A summary of these results is given in table 1.

In individuals with testicular insufficiency, more than in normal men, all of the steroids under trial, except estradiol propionate, increased the threshold of the susceptibility of blood vessels to deprivation of oxygen. The deprivation of oxygen was obtained by complete circulatory stasis from a ligature applied to the arm.

Testosterone propionate caused a marked increase in the finger volume of castrate men. This action was not seen in the normal or in the eunuchoid men. Desoxycorticosterone acetate, progesterone, and estradiol propionate exerted no detected effects on finger volume in castrate or in eunuchoid individuals. Only estradiol propionate increased finger volume in the normal men.

#### CONCLUSIONS

Significant differences exist between the dermo-

vascular actions of estrogen and testosterone propionate. Androgens and estrogens exert demonstrably different effects upon the blood vessels of the skin. The reactions, in part at least, apparently affect different regions of the vascular tree, and depend also upon the degree of gonadal insufficiency at the time of injection. In castrated males, there are fluctuations in excitability of the smallest blood vessels of the skin which greatly exceed those found in normal subjects. These fluctuations not only exceed by a wide margin the relatively small changes in excitability noted in normal men, but are also characterized by suddenness of appearance and disappearance as well. Finally, correlations made with previous spectrophotometric studies (4) of blood in cutaneous vessels show the increase of hemoglobin in the skin after injection of testosterone to be coupled with transient vasodilatation and diminished excitability of the smallest blood vessels of the skin.

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# Clinical Use of Testosterone in the Male Climacteric

## {Testosterone Therapy}

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MARK J. MARKHAM, M.D.

THE MALE CLIMACTERIC presents one of the complex problems of aging. Its etiology is confused and undetermined. Its symptomatology is involved, tremendously varied, and rarely brought to the attention of the physician in all its diversity. This latter fact is so, because of the very diversity of these symptoms and because of the apparent lack of relationship between the various physiologic systems involved. Treatment of this state is still in its earliest trial stage.

No definite set of criteria for determining the age limits of the climacteric state has been developed. Limits range from Havelock Ellis' description of the onset of the 'critical age' at 38, to any decade thereafter. Certainly, copulatory frequency is no criterion of the climacteric since Pearl's data on such frequency indicated a high variability—8 to 10 times as variable as data for body weight. And although, according to Engle (1), sex impotence is a concomitant of the aging process, the variability of this symptom is too great to permit its use as a sole criterion. Moore (2) believes that old age as determined by the morphology of the prostate may be considered definite at sixty years. However, only 4 of every 10 males showing such definite morphological changes of the prostate will show any signs of obstruction. The signs and symptoms of prostatism *per se*, therefore, cannot serve as criteria in determining the presence of the male climacteric.

From a hormonal point of view, additional difficulties present themselves. No phenomenon equivalent to the female menopause can be demonstrated in the male. There is no sharp decline in reproductive capacity within any one limited period. Nor is there, at any given time, a marked increase in the excretion of gonadotropins such as is demonstrable in women.

The menopause is one of the many signs of the aging of the female genital organs. Strictly speaking, the menopause means the final cessation of menstruation. Before this takes place, irregularities in menstrual rhythm and a whole group of neurocirculatory symptoms appear. These symptoms plus added

psychic phenomena may persist for several years after complete cessation of menstruation. The term climacteric is used to embrace not only the menopause, but the whole symptom complex occurring during this period.

It is in this sense that the term climacteric may be applied to the male—as a period in life. In the same sense, although we cannot use impotence or the symptoms of prostatism or neurocirculatory disturbances individually as criteria for establishing the definite presence of endocrine imbalance, the related presence of all or some of these symptoms in a patient are indicative that we may be dealing with the male climacteric.

The symptoms of the male climacteric can, therefore, be grouped under four clinical headings: a), Neurocirculatory, b), psychosexual, c), genito urinary and d), miscellaneous. The neurocirculatory symptoms include all those that may be observed in the female climacteric. These are hot and cold flashes, excessive perspiration, palpitation, dizziness, tingling, headaches and cardiac angina.

Clinically, it is rare to find the various anxiety states and other mental disturbances dissociated from the presence of decreased libido and partial or complete impotence. For this reason, it would appear best to link these phenomena under one category—the psychosexual.

The genito urinary symptoms of frequency, nocturia, dribbling, inability to start the urinary stream and occasional dysuria are almost invariably associated with changes in the prostate and seminal vesicles—particularly with benign prostatic hypertrophy.

Among the miscellaneous symptoms can be included muscular aches, fatigue not attributable to the cardiovascular and other systems and the accumulation of lower-trunk fat (3).

It has been established that the ovarian hormones are necessary to maintain the female reproductive organs in good physiologic state. In the female, estrogenic substances play an important part in maintaining the water balance and the vascularization of the genital tissues—factors which are of fundamental importance in the study of the causes of aging. A



similar relationship exists between the testis and the male genital tissues. According to Engle, atrophy of the prostate and seminal vesicles occurs following castration in all mammals, including man. Senile involution or atrophy seems to depend on the complete absence of the testis hormone. This would offer no explanation for the preponderance of benign prostatic hypertrophy in the fifth and later decades. To explain this state, Zuckerman (4) and Laqueur (5) have posited an imbalance between androgens and estrogens—the decrease in androgen during the climacteric enabling uninhibited estrogenic substances to produce prostatic hypertrophy. It is interesting to find in this connection that in 1936, Zuckerman (4) experimentally produced prostatic hypertrophy in monkeys by injecting estrogenic hormones. On the other hand, Lower, Engle and McCullagh (6) believe that the testis hormones have a fraction which decreases the prostate size by inhibiting the pituitary. During the climacteric, when there is a decrease in androgens, this inhibiting influence would disappear permitting the prostate to hypertrophy. This substance was called 'inhibin' by these investigators. In any case, some relationship between the hormonal state in the climacteric and benign prostatic hypertrophy does appear to exist. Working on this assumption, numerous investigators, including among others Zuckerman and Greene (7), Cary (8), Dix (9), Douglas (10), Bolend (11), and Day (12), have been clinically able to relieve in varying degrees the symptoms of prostatism by the use of testosterone propionate.

It was inevitable that, following successful replacement therapy in castrates, eunuchoids and youthful hypogonads, attempts should be made to treat the impotence associated with the male climacteric. McCullagh (13), Dunn (14), Hamilton (15) and Douglas (10) have reported the successful restoration of potency in the male climacteric by the use of testosterone propionate. Psychic disturbances and changes in the general physical state provide too confusing a complication to permit adequate evaluation of these results. Carmichael and Noonan (16), who treated 18 impotent men with androgens and obtained good results in 7 considered these good results as psychological in origin.

In the female, estrogenic substances have been found to give symptomatic relief of a wide variety of neurocirculatory symptoms occurring in and about the time of the female menopause. Reynolds and Forbes (17), working with estrogens in males have been able to produce definite dilatation of the skin vessels, establishing the vascular effect of these substances. Using the hypotheses of Zuckerman (4) and Laqueur (5) concerning androgen and estrogen imbalance, at least a tentative explanation of the hot

and cold flashes and excessive perspiration seen in the male climacteric can be offered. From a clinical point of view, however, Bonnell, Pritchett and Rardin (18) have attributed vasodilatory properties to both estrogenic and androgenic hormones. These workers treated 23 patients having cardiac disease. Of the 23, 18 were men. Of these 18, 5 received androgens alone, 11 were given estrogens and 2 received both androgens and estrogens. Complete relief was obtained in 4 of these men and good to excellent results in 13 of them. Fewer anginal attacks occurred and fatigue and dyspnea decreased. The results were essentially similar whether estrogens or androgens were used. Here too, whether we are dealing with the re-establishment of some endocrine balance, or direct substitution therapy, some relationship does seem to exist between various neurocirculatory disturbances and the hormonal state preponderantly found in the climacteric.

We feel convinced that there is an imbalance of internal secretion in those men presenting various combinations of the above described symptom groups. And, since we feel that this imbalance is analogous to that which is so successfully treated in women with estrogenic substances, we have selected the following eight cases and treated them with testosterone propionate<sup>1</sup> after being convinced that, in so far as the cardiovascular symptoms were concerned, there was no organic pathology present. The first of this series of cases was carefully followed and treated both on the wards of the Bronx Hospital and in the Endocrine Clinic of the Bronx Hospital. Cases 2, 3, 4, 5 and 6 were selected from the private practice of one of us (S.F.G.), and the last two cases were selected from the private practice of the other (M.J.M.).

#### CASE REPORTS

*Case 1.* I.H., age 55 was admitted to the Bronx Hospital July 30, 1940, with complaints of attacks of precordial pain of 6 years' duration. His past history was negative except for tonsillectomy and appendectomy and a trace of sugar found in the urine in November, 1939. Six years prior to admission the patient began to develop recurrent, gripping, non-radiating precordial pain. These pains appeared at rest and without effort and had begun to occur more frequently in the 3 months prior to admission to the hospital. On July 26, 4 days before admission, the patient experienced a very severe attack lasting 1 hour. The pain was associated with dyspnea. In the next few days, repeated attacks of precordial pain, radiating down the right arm and occasionally down the

<sup>1</sup> Testosterone propionate (Oreton) used with the first 6 patients, was supplied by Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J. Case 7 received oral methyl testosterone (Neo-Hombreol (M) tablets). The products used in case 8 (Neo-Hombreol ampoules and Neo-Hombreol (M) tablets) were supplied by Dr. L. Pirk of Roche-Organon, Nutley, N. J.

left arm occurred. The patient complained of dyspnea with the slightest exertion. The only other complaints were referable to the genito-urinary tract. There was frequency of urination, 3 to 4 times during the day with no dysuria. There was no impotence.

On admission, the patient looked obese and not acutely ill in appearance. There was no dyspnea. Lips showed a suggestion of cyanosis. Pupils were equal and reactive. The thyroid was not palpable. The lungs were clear to percussion and auscultation. Heart sounds were muffled. The point of maximum intensity was in the sixth interspace in the midclavicular line. No apical impulse or thrill was palpable. He had regular sinus rhythm. Blood pressure was 110/70 mm Hg. The physical findings on examination of the abdomen and extremities were negative.

Laboratory examination showed a negative urine with good concentration. Blood chemistry revealed glucose 104.7 mg per cent, urea 14.7 mg per cent, uric acid 3.5 mg per cent, creatinine 1.03 mg per cent. Hemoglobin was 110 per cent, red blood cells 5,100,000, white blood cells 10,400 with 65 per cent polymorphonuclear leucocytes. Sedimentation rate was increased. An electrocardiogram taken on the day after admission showed no evidence of myocardial disease. Roentgenograms of the spine revealed a hypertrophic osteoarthritis of the cervical and dorsal spine. Basal metabolic rate was minus 18.

The temperature of the patient was normal on admission and persisted normal throughout his stay. On admission, he was placed on 1/150 grain of nitroglycerine for pain. In spite of repeated use this failed to give any relief. In view of the essentially negative clinical findings and the probability that we were dealing with the climacteric period and its varied complications, the patient was placed on 25 mg of testosterone propionate, administered intramuscularly every other day. By the end of the second week he stated that he felt much improved and that he was able to walk around with very little pain and no shortness of breath.

Three weeks after his admission to the hospital, the patient was discharged improved and was referred to the Endocrine Clinic where injections of 25 mg of testosterone propionate were continued 3 times a week. A second electrocardiogram taken in the clinic showed no evidence of myocardial damage. The patient continued well on treatment, his only complaints being slight angular pain. At the end of 4 months of treatment, injections were reduced to twice weekly and one month later to once weekly. He continued ambulatory and improved for an additional two months and then he began to complain of increased dizziness, weakness and precordial pain. In order to determine the possible effect of a placebo on the patient, his injections were increased to twice weekly. However, ampoules of sesame oil were substituted for testosterone propionate. At the end of one month, because of persistence of marked complaints, placebo treatment was increased to 3 times weekly. Two weeks later he was complaining of marked weakness, dizziness, insomnia, and severe recurrent angular pain. His basal metabolic rate at this time was minus 11. Therapy was now changed back to 25 mg of testosterone propionate, injected 3 times weekly. At the end of one month he felt

much stronger and complained much less of pain. Treatment 3 times a week was continued for another month and a basal metabolic rate taken at this point was minus 4. However, despite testosterone propionate, the patient began to complain once more of chest pain, fatigue and dizziness. All treatment was, therefore, discontinued and within 2 weeks he felt much worse than at the time of the stopping of treatment. Once again, instead of returning to testosterone propionate, the patient was placed on sesame oil injected 3 times a week. Although he thought he felt better after the first week of this placebo therapy, at the end of the second week he felt much worse. He complained of generalized muscular pains, severe precordial pressing and shortness of breath. He was kept on sesame oil, but failed to show improvement. Testosterone propionate therapy twice a week was, therefore, resumed a third time and once again clinical improvement was observed with marked symptomatic relief. This time, testosterone propionate therapy was maintained for two months and then discontinued. Throughout the time the patient was under treatment, nocturia 2 to 3 times and frequency 4 to 5 times persisted unchanged. At about the time when all treatment was discontinued, frequency and nocturia became more marked and dysuria associated with suprapubic pain developed. Cystoscopy revealed hypertrophy of the prostate and a papilloma of the bladder just behind the left ureteral orifice. Since fulguration of the papilloma, dysuria and suprapubic pain have disappeared and there is nocturia one time. The patient, in the meantime, is ambulatory and attending to his work.

**Case 2** T S, 63 years of age, in whom a diagnosis of angina pectoris sine dolore had been made 20 years previously, had weakness and precordial distress, but no definite pain. At one time the electrocardiogram revealed myocardial damage. Since then, he has had five or six attacks of angina pectoris and has been confined to bed for periods of from several days to several weeks. Following these seizures, repeated electrocardiograms were negative. At the time he was selected for treatment, he complained of precordial pain on exertion (occasionally while at rest). He had hematuria on one occasion, probably due to a ureteral calculus which was passed. Laboratory data were negative. His blood pressure was 140/90 to 150/90 mm Hg. In July, 1939, while he still complained of general weakness and precordial pain, he was given testosterone propionate (3 injections a week, 25 mg per injection), for 10 weeks. Following this he suffered a severe angular attack and was bedridden for several weeks. Treatment was then resumed. For a period of 2 months he felt better, had no attacks, and was free from pain for the first time in many years. His blood pressure rose to 175/90 mm Hg while under treatment. When he suffered another attack, treatment was discontinued.

This patient has attacks as frequently as before therapy and has not responded to the treatment.

**Case 3** A G, a 65 year old physician, had had typhoid and erysipelas many years ago. Otherwise he had never been ill. In July, 1930, he began to experience precordial discomfort at times. During that period his blood pressure, electrocardiogram, urine and other laboratory data

were negative. In 1937, after a heavy meal, he felt a sudden pressure in the precordium, and felt very weak and dizzy. He was given 1/100 grain of nitroglycerine and was relieved. There was no further trouble for some time. Then symptoms typical of angina pectoris began to return. At times he had arrhythmia and extra systole. Nitroglycerine was used with good effect. At times 2 or 3 doses a day were taken. He could not walk more than 200 or 300 feet without taking nitroglycerine. He was very irritable, suffered from anorexia and intermittent claudication, especially while in bed. He also complained of general muscular aches and pains.

In 1939 he received several injections of testosterone propionate. After 3 injections the precordial pain became considerably less frequent and less severe. As treatment proceeded (2 injections a week), his bodily vigor increased and he could walk several blocks without any discomfort. The dosage of testosterone propionate was gradually decreased to 25 mg. once a week, then once in 2 weeks and then once in 6 weeks, to the present.

He now carries on his medical practice without any difficulty, having no dyspnea and very infrequent precordial pain. He uses no nitroglycerine, and receives 25 mg. of testosterone propionate once in 5 to 6 weeks. The leg pains have disappeared and he is very comfortable.

Case 4. S.A., a practicing dentist, 60 years of age. He had had pulmonary tuberculosis which was arrested 25 years ago. Every now and then he complained of weakness and gastric disturbance. He also had suffered from muscular pains in the legs. He was well preserved, weighing between 180 and 190 pounds. The findings upon physical examination, including an electrocardiogram, were negative.

In May, 1939, he complained of dizziness, irritability, inability to walk more than a block without experiencing cardiac pain, and the fact that he could not stand at work. His blood pressure was 150/75 mm. Hg, pulse 80, regular and of good quality, his cardiac sounds somewhat distant. The lungs were negative except for a healed lesion. The abdominal examination and all laboratory data were negative.

He was given testosterone propionate, 25 mg. 3 times a week at first, and later twice a week and improved considerably, so much, as a matter of fact, that he discontinued treatment for 6 weeks, whereupon, all of his symptoms returned. He then received for 3 months, once a week, 25 mg. of testosterone propionate. Treatment was stopped in the middle of 1940. Since then, there have been no complaints referable to his heart.

Case 5. N.G., a cutter by occupation, 66 years of age, had never had any serious illness. He had been under the routine observation of a physician for 10 years. His weight has always been between 146 and 152 pounds. His blood pressure ranged between 145/70 and 160/80 mm. Hg. The urine and blood examinations were negative.

In 1932 he began to complain of precordial pressure, irregular muscular pains, and restiveness. His heart was negative on physical examination.

In 1937 he complained of shortness of breath and precordial pressure. His blood pressure was 150/75 mm. Hg.

In January, 1939, he started to complain of more precordial pressure and dyspnea. He could not walk more than one block. His weight was 146 pounds, blood pressure 140/65 mm. Hg, heart negative. He was very irritable, cried easily and for no reason, and felt depressed. He could not walk without a cane.

In June, 1939, he was started on testosterone propionate therapy, 25 mg. 3 times a week. Within a short time he claimed that he felt much better and walked as much as a mile without any dyspnea or fatigue.

In May 1940, the patient returned complaining of repeated anginal attacks. He was given a series of injections of 25 mg. of testosterone propionate once a week for 3 months. During this period he worked only 3 days a week. He improved considerably and stopped complaining of pain. Since then, he has retired, lives in the country and takes care of a small garden. There are no complaints of pain or fatigue.

Case 6. H.S., business man, 61 years of age. His past history reveals a left nephrectomy in 1907 for calculus-pyonephrosis. There was a 3-year history of recurrent precordial pain, pressing in nature, occasionally radiating to the right or the left or to both shoulders. He had dyspnea with moderate exertion associated with marked afternoon fatigability, lassitude and dizziness. In recent months the patient had become increasingly despondent, feeling that everything was wrong with him. For a period of the last 6 months (fairly coincident with his depressive state) the patient had developed nocturia 3 to 4 times and frequency 6 to 7 times. The urinary stream was very narrow and the patient dribbled markedly, persistently soiling himself. There had been no erections for a period of about 4 years. Physical examination showed moderate obesity, marked arcus senilis. Heart sounds were good, point of maximum intensity was in the fifth interspace in the midclavicular line, blood pressure 140/80 mm. Hg. There was an umbilical hernia and the prostate was smooth, firm and moderately enlarged. Intravenous pyelogram revealed a negative right kidney and an enlarged prostate. An electrocardiogram showed no evidence of myocardial damage. This patient was started on 50 mg. of oral methyl testosterone daily (5 doses daily) and treatment was continued in this way for 3 months. After the first 6 weeks of treatment, the patient showed a marked general physical improvement. He stated that he was able to wait upon customers in his store throughout the day with very little fatigue. Although nocturia 2 times and frequency 4 to 5 times were present, dribbling and soiling of underclothes had disappeared. Attacks of precordial pressing pain occurred less frequently and could often be ignored by the patient when they did occur because of the decrease in intensity. Associated with these changes in his physical state, there was a gradual disappearance of his fits of depression. At present, although treatment has been discontinued for 2 months, the patient appears bright, is able to work without precordial pressing pain, dyspnea or fatigue. Nocturia one time persists. There is no dribbling or frequency.

Case 7. S.S., age 63, widower. His past history reveals that he suffered from frequency, nocturia, dribbling, and

a narrow urinary stream of 5 years' duration. Two years ago a pressing, precordial pain unrelated to exertion and non radiating in character appeared. In June, 1939, because of the severity of his urinary symptoms, a two stage prostatectomy was performed. The wound healed completely. However, nocturia 2 to 3 times, dribbling and soiling of clothes persisted following the operation and showed no signs of decrease. Six months after the operation, the patient began to complain of increasing fatigue, precordial pressing attacks lasting 10 to 20 minutes and occurring 2 to 3 times a day, and dyspnea associated with the precordial pressing. Despite the fact that the patient was constantly troubled by thoughts of sexual intercourse, he found that erections were incomplete at this time, or else that ejaculation occurred prematurely. Physical examination revealed no apparent cardiac enlargement. Heart sounds were good, pulse rate 76 and blood pressure 150/100 mm Hg. Fluoroscopy showed no evidence of enlargement of the heart and an electrocardiogram showed no evidence of myocardial damage. There was a healed suprapubic wound. The prostatic bed showed no evidence of prostate tissue. Urine examination was negative except for a trace of sugar. Fasting blood sugar was 87 per cent. A gastric series taken on this patient was negative.

The patient was started on 10 mg of oral methyl testosterone 5 times daily. This treatment was continued for 6 weeks. At the end of this time there was no apparent change in the patient's symptoms. Oral methyl testosterone was, therefore, discontinued and the patient was placed on 25 mg of testosterone propionate, intramuscularly, 3 times weekly. At the end of 3 weeks of treatment, the patient showed improvement in both his cardiovascular and urinary symptoms. Dribbling disappeared, nocturia occurred 1 to 2 times. The cardiovascular change was much more marked. Fatigue and precordial pressing became so mild, that the patient began to consider seriously remarriage. However, during this initial period of 3 weeks, all erections disappeared, and the patient definitely associated this phenomenon with his treatment. Injections of 25 mg of testosterone propionate were continued 3 times weekly. The patient continued to show a steady improvement in his physical state by his activity and marked decrease of cardiac and muscular complaints. Nocturia one time persisted. At the end of 7 weeks of injections, occasional erections recurred with completion of the sexual act. Injections were decreased to one time weekly and on this dosage the patient had been maintained to date in this improved state.

#### DISCUSSION

It will be noted that in all these cases, the patients to a greater or less degree, complained of an effort syndrome. Likewise, they all suffered from climacteric symptoms—weakness, muscular aches and pains, irritability, lachrymosity, and restlessness, as well. In no patient (with the exception of case 2), was there at any time evidence of myocardial disease as determined by the electrocardiogram. None of them had

hypertension (with the same exception) or showed any nephritic changes. All of these symptoms are typical of the climacteric in women. Warner (19), in 1939, described two cases of what he considered climacteric in the male, both of whom not only had tachycardia, dyspnea, and palpitation, but also flushes. They were completely relieved by testosterone propionate. He reminds us that tachycardia, palpitation and dyspnea occurred in 69 per cent of 197 cases of female climacteric which he had studied. That symptom complex, as a matter of fact, occurred 9th, in 21 symptoms of the female climacteric listed in order of their frequency.

Case 2 (BS), who at one time did show electrocardiographic evidence of myocardial damage, had in recent times had repeatedly negative electrocardiograms. Under treatment, he improved temporarily, but he did experience severe attacks while he was receiving testosterone propionate. He is, at present, getting these attacks as often as and severely as before. This case did not show any favorable result.

Case 4 (SA) is important for the reason that when the patient discontinued the treatment for 6 weeks, his symptoms returned, and when treatment for 6 weeks, his symptoms returned, and when treatment was resumed, the patient improved again. It might be said that the result was due to the psychic effect of the injections. If this is so, it is truly remarkable, since trained psychiatrists have attempted to treat patients in the climacteric with not nearly as signal a success.

Case 1 provides the best refutation of the assumption that we are dealing with the psychological influence of injections and treatment. Repeatedly placebos failed to produce the symptom relief that testosterone was able to give this patient.

In cases 7 and 8, although methyl testosterone orally was able to give satisfactory relief of the neurocirculatory symptoms of case 7, no apparent effect of this apparently potent oral preparation was observed in case 8. Case 8 did respond satisfactorily, however, to testosterone propionate administered intramuscularly.

It is not our intention to place the responsibility for the symptom of angina pectoris in the male climacteric on the absence or presence of any single hormone. We do maintain that an endocrine imbalance is very likely responsible, just as it may be for the frequent peripheral vascular phenomena which may occur during the climacteric. Incidentally, reports of the benefits of testosterone propionate in many peripheral vascular conditions are becoming more frequent. It seems quite possible to us that intermittent claudication and angina pectoris are not far removed from each other in etiology, especially in respect to this age group.

We wish to urge the careful study of men from 50 to 65 years of age when they complain of vague and often apparently unrelated symptoms, for evidence of the climacteric, and a subsequent use of testosterone propionate, in an attempt to relieve their suffering.

#### SUMMARY

Seven cases of effort syndrome, considered by us as a complication of the climacteric and treated with testosterone propionate have been reported. Of these cases, 6 responded favorably, and one, which was a true cardiac, did not respond.

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# Effect of Androgens on the Blood Count of Men

## [[Androgens and Blood Cells]]

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**E**UNUCHOID PATIENTS treated actively with testosterone propionate or methyl testosterone<sup>1</sup> frequently develop a rather striking increase in energy and a plethoric appearance. The observation of such changes led us to make serial determinations of the erythrocyte, hemoglobin, hematocrit and leucocyte levels of the blood and to attempt to correlate such changes as might occur with the basal metabolism.

When it was realized that a distinct rise in red cell count and hemoglobin followed the use of androgens in certain cases, blood counts which previously had been made at random were also correlated with previous therapy where possible. These are included in cases 1 to 4.

The data reported here were obtained on 12 patients. The shift of blood count in one of these has been reported (1) previously (case 3). Of these 12, eight were eunuchoids without evidence of pituitary disease, two had signs of pituitary disorder, one dwarfism and one roentgenologic evidence of pituitary or suprasellar neoplasm, two were sexually mature males with impotence. Four of the 8 eunuchoids without evidence of pituitary disease had received testosterone propionate intramuscularly for periods of two to three years and methyl testosterone subsequently, four were treated with methyl testosterone for periods of four to eighteen months and had had no previous androgen therapy. The pituitary cases and the mature males were treated chiefly with methyl testosterone orally.

In the charts and tables, routine blood counts made in the laboratory are represented where only erythrocyte count and hemoglobin are given, special counts made in the hematology research laboratory are represented where erythrocyte count, hemoglobin and hematocrit readings are shown. A Haden Hauser hemoglobinometer was used. The basal

metabolic rates were calculated by the Boothby and Sandiford (2) modification of DuBois and DuBois standards. Two runs constituted one test.

### RESULTS

The results are shown in the accompanying figures and tables. The data in figure 1 and tables 1, 2 and 3 show some long term effects of testosterone propionate on the erythrocyte and hemoglobin levels, and their relation to the BMR. In all cases methyl testosterone therapy was employed during part of the period of observation. Figure 1 shows the effect of methyl testosterone on the blood of a patient already made relatively mature sexually by the use of testosterone propionate. Figures 2 and 3 illustrate the effects of methyl testosterone on untreated eunuchoids. The data in tables 8 and 9 show erythrocyte, hemoglobin and hematocrit levels and BMR changes in two sexually mature, functionally impotent males receiving methyl testosterone. The years of age shown in the charts refer to the present.

**Case 1** (fig. 1) was 24 years of age in 1936. He had severe eunuchoidism which had followed bilateral testicular atrophy occurring after attempted orchidectomy at the age of 11 years. During 1937 and 1938 testosterone propionate had led to a degree of maturity approximating average normal for 18 or 19 years of age. A slight rise in blood count and BMR occurred under testosterone propionate therapy and there is a suggestion of a fall upon withdrawal, but in neither blood count nor metabolic rate were the shifts pronounced enough to be definite on the other hand, the rise in both blood count and metabolism in response to methyl testosterone was quite marked, and the changes are parallel insofar as the data show. The blood count had fallen after the hormone had been withheld for one month in 1941. The blood count on February 3rd showed 5.81 million erythrocytes, 107 per cent hemoglobin, hematocrit 50 cc per 100. Therapy was discontinued on February 21 and on March 21 the count showed a blood count of 5.59 million red cells, 91 per cent hemoglobin, hematocrit 46 cc per 100 cc.

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<sup>1</sup> The testosterone (Oreton M) is courtesy of I. Schering Corp., Bloomfield, N. J.

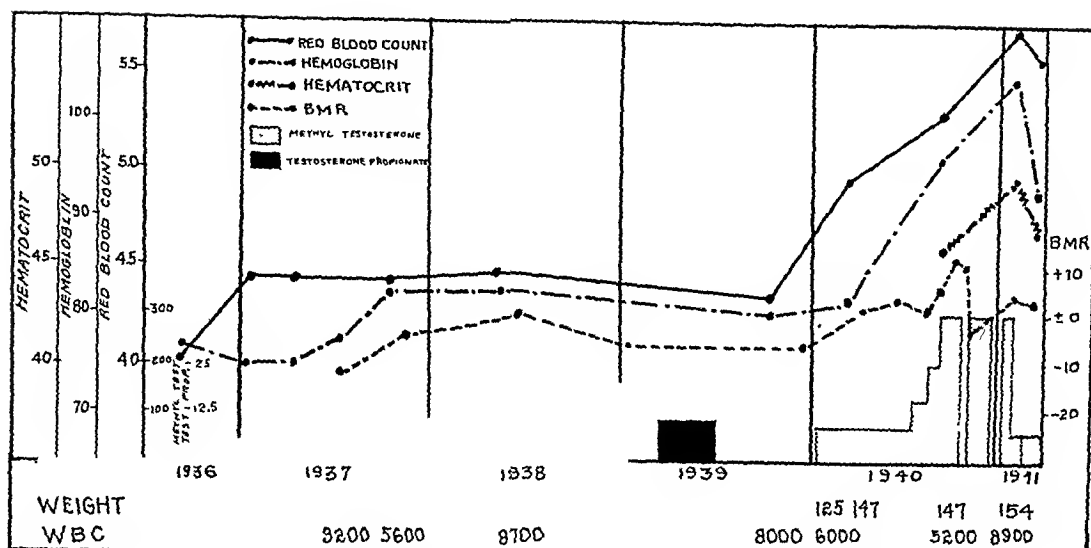


Fig. 1. EFFECT OF ANDROGENS ON BLOOD COUNT OF EUNUCHOID, case 1, AGE 28.

There was no rise in leukocytes accompanying the rise in red cell numbers, and as the erythrocyte and hemoglobin levels increased the body weight also increased by 25 pounds, indicating that none of the rise in red cell count could be explained on a basis of blood concentration.

Case 2, (table 1), was one of severe eunuchoidism. Sexual maturation progressed strikingly on androgen therapy. There was a parallel rise of blood count and basal metabolism while he was receiving testosterone propionate. Under methyl testosterone therapy in 1940, the blood count and B.M.R. were considerably

TABLE 1. Case 2, EUNUCHOID, AGED 33

| Date     | Weight | R.B.C.  | Hemo-globin | Hemato-crit | Leuco-cytes | B.M.R. | Therapy<br>Test. Prop. Methyl Test. |
|----------|--------|---------|-------------|-------------|-------------|--------|-------------------------------------|
|          | lb.    | million | %           | cc./100 cc. |             | %      | mg. per day                         |
| 12/17/36 | 162    | 4.50    | 78          |             | 8200        | -24    | 5, begun                            |
| 3/1/37   | 165    | 4.60    | 80          |             | 7450        | -13    |                                     |
| 7/19     | 164    | 4.85    | 87          |             |             | -15    |                                     |
| 10/15    |        | 4.80    | 84          |             | 6100        |        | 25, begun                           |
| 5/5/38   | 171    | 5.00    | 83          |             | 5600        | -6     |                                     |
| 12/6     | 170    | 5.16    | 91          | 43          | 6250        | -4     | Stopped,<br>av. 10 <sup>2</sup>     |
| 3/1/39   |        |         |             |             |             |        |                                     |
| 3/29     |        |         |             |             |             |        |                                     |
| 1/2/40   |        |         |             |             |             |        | Increasing<br>from 50 to 250        |
| 1/29     |        |         |             |             |             |        |                                     |
| 7/4      |        |         |             |             |             |        | Stopped                             |
| 8/15     | 166    | 5.70    | 97          | 49          | 9900        | +13    |                                     |
| 9/9      | 163    | 5.50    | 94          | 49          | 11000       | -9     |                                     |
| 9/18     |        |         |             |             |             | +4     | 250, begun                          |
| 10/28    |        |         |             |             |             | +16    | Stopped                             |
| 11/18    |        |         |             |             |             | +7     | 300, begun                          |
| 12/3     | 172    | 5.50    | 94          | 48          | 7750        | +28    | Stopped                             |
| 12/20    | 170    | 5.50    | 91          | 46          | 8000        | +21    |                                     |
| 1/10/41  |        | 5.34    | 87          | 43          |             | -14    | 500, begun                          |
| 1/21     | 161    | 5.36    | 91          | 47          | 8200        |        | Stopped                             |
| 1/27     | 160    | 5.26    | 87          | 45          |             | +3     |                                     |
| 1/30     |        |         |             |             |             |        | 25, begun                           |
| 2/14     |        |         |             |             |             |        | 50, begun                           |
| 2/17     | 170    | 5.36    | 87          | 45          | 8300        | +7     |                                     |
| 3/5      | 173    | 5.60    | 91          | 48          | 6950        | +5     |                                     |
| 7/1      |        |         |             |             |             | +3     | Stopped                             |
| 7/24     | 180    | 5.05    | 84          | 44          |             | -13    | 50, begun                           |
| 8/14     |        |         |             |             | 7600        | -6     | 100, begun                          |
| 9/8      |        | 5.40    | 91          | 48          | 6300        |        |                                     |
| 12/—     | 193    | 5.83    | 94          | 53          |             |        |                                     |

<sup>1</sup> Basal determination on 12/12/40.

<sup>2</sup> In addition to two 200 mg. implants of testosterone propionate.

higher than under testosterone propionate. The blood count did not fall as rapidly as the metabolic rate on withdrawal of treatment in December, 1940. They were not raised appreciably by ten days of intensive methyl testosterone therapy in January, 1941. After an interval of ten days without treatment, testosterone propionate therapy produced a slight rise in blood count, which may represent some degree of summation.

In this as in other cases it will be seen that the weight rose with therapy while the blood count was

Case 3 (table 2). In this case severe hypogonadism followed mumps at 13 years of age. The androsten mentioned was an androgenic urinary extract of low potency. No change in blood count or BMR accompanied its use. During 1938 while testosterone propionate was being used, the metabolic rate and blood count rose, the metabolic rate falling again after its withdrawal. It should be noted that in this case no blood count is recorded between November, 1938, and August, 1940. Testosterone propionate was discontinued in October, 1939, following which the

TABLE 2. Case 3, EUNUCHOID, AGE 41

| Date       | Weight | RBC     | Hemo-<br>globin | Hemato-<br>crit | Leuco-<br>cytes | BMR | Therapy<br>Test Prop | Methyl Test               |
|------------|--------|---------|-----------------|-----------------|-----------------|-----|----------------------|---------------------------|
| March, '33 | lb     | million | %               | cc/100 cc       |                 | %   |                      | mg per day<br>(Androsten) |
| August     | 152    | 4.54    | 81              | 38              | 4950            | -28 |                      |                           |
| June, '34  | 150    | 4.01    | 71              | 34              | 5050            |     |                      |                           |
| Dec., '35  | 166    | 4.28    | 71              | 36              | 5100            |     |                      |                           |
| 1937       |        | 4.40    |                 |                 | 7600            | -27 |                      |                           |
| 3/1/38     |        | 4.20    | 72              |                 | 6550            |     | 25, begun            |                           |
| 7/20       |        |         |                 |                 |                 |     | 50, begun            |                           |
| 9/20       |        | 5.04    | 84              | 46              | 6800            |     | 25, begun            |                           |
| 10/3       | 202    | 5.00    | 94              | 46              | 8400            | -18 | 50, begun            |                           |
| 11/30      |        |         |                 |                 |                 | -17 |                      |                           |
| 12/6       | 198    |         |                 |                 |                 |     | 25, begun            |                           |
| 2/8/39     |        |         |                 |                 |                 |     | Stopped              |                           |
| 10/10      |        |         |                 |                 |                 | -29 |                      |                           |
| 2/23/40    | 194    |         |                 |                 |                 | -15 |                      | 50, begun                 |
| 3/27       |        |         |                 |                 |                 | -15 |                      | 100, begun                |
| 8/7        | 207    | 5.30    | 94              | 48              | 6050            | -6  |                      |                           |
| 9/24       | 203    | 5.30    | 91              | 49              | 5650            | -8  |                      | 150 begun                 |
| 11/12      | 200    | 5.60    | 100             | 51              | 6900            | -6  |                      | Stopped                   |
| 12/3       | 192    | 5.10    | 91              | 44              | 5850            | -2  |                      |                           |
| 12/16      | 190    | 5.00    | 94              | 42              | 5250            | -22 |                      | 60, begun                 |
| 1/28/41    |        |         |                 |                 |                 |     |                      | Stopped                   |
| 4/2        |        |         |                 |                 |                 |     |                      | 50, begun                 |
| 4/12       | 190    | 4.90    | 91              | 44              |                 | -13 |                      |                           |
| 8/2        |        | 4.80    | 84              | 45              | 7700            |     |                      |                           |

rising and fell on withdrawal of therapy when the blood count fell. This would appear to exclude a concentration dilution effect and to render the increase in blood count more significant. In this case an exception to the rule regarding weight shift occurs during the use of very high doses of androgens in January, 1941. This can be explained on the basis of the limited caloric intake which was imposed during a time when certain metabolic studies were being made. The white blood count suggests no concentration—dilution effect, being the same with low red counts in 1936 and 1937 as during high ones in 1940 and 1941.

In case 2 during January, 1941, reticulocyte counts were made frequently, methyl testosterone in doses of 500 mg per day orally being used from January 11 to 20th inclusive. The reticulocyte counts were as follows:

January  
Reticulocytes, % 8 9 11 14 17 18 21 23 24 27  
0.6 0.5 0.7 0.7 0.7 0.5 0.6 0.5 0.7 0.7

BMR fell to minus 29 per cent before the use of methyl testosterone was begun in February, 1940. The blood counts shown indicate no shift between 1938 and 1940, but in the light of the other data presented it seems reasonable to assume that a considerable fall in blood count occurred and was corrected again by August, 1940.

In 1940 a rise in metabolism of about 23 per cent accompanied the use of methyl testosterone and had not fallen in three weeks but did so within five weeks after cessation of therapy. A shift in hemoglobin and hematocrit levels is seen to accompany this reduction of the BMR. This case is of particular interest because the anemia had been shown to be persistent over a long period of time prior to effective androgen therapy in spite of the fact that iron medication, usually in the form of Bhud's mass or reduced iron in doses of 30 grams per day had been given during much of the time between 1933 and June 1, 1937. Since June, 1937 no iron medication or any other



TABLE 3. Case 4, EUNUCHOID, AGED 35

| Date     | Weight | R.B.C.  | Hemo-<br>globin | Hemato-<br>crit | Leuco-<br>cytes | B.M.R. | Therapy<br>Test. Prop. Methyl Test. |
|----------|--------|---------|-----------------|-----------------|-----------------|--------|-------------------------------------|
|          | lb.    | million | %               | cc./100 cc.     |                 | %      | mg. per day                         |
| 12/24/36 | 140    |         |                 |                 |                 | -21    |                                     |
| 4/15/37  |        | 3.90    | 78              |                 | 5400            |        | 5, begun                            |
| 12/9     |        |         |                 |                 |                 |        | 12.5, begun                         |
| 2/8/38   |        | 5.50    | 96              |                 | 11200           |        |                                     |
| 5/21     | 150    |         |                 |                 |                 | -3     |                                     |
| 7/30     |        |         |                 |                 |                 |        | 25, begun                           |
| 4/15/39  |        |         |                 |                 |                 |        | Stopped                             |
| 7/19/40  | 146    | 4.20    | 81              |                 | 4350            | -20    |                                     |
| 7/28     | 143    |         |                 |                 |                 | -28    |                                     |
| 8/8      | 148    |         |                 |                 |                 | -13    | 200, begun                          |
| 8/27     | 156    |         |                 |                 |                 | -1     |                                     |
| 9/14     | 168    |         |                 |                 |                 | +4     | 100, begun                          |
| 10/12    | 175    | 5.10    | 95              |                 | 5750            | +12    | 200, begun                          |
| 11/16    | 178    | 5.50    | 100             |                 | 7050            | +21    | 300, begun                          |
| 1/14/41  | 165    | 5.40    | 91              | 46              | 4850            | -10    | Stopped                             |
| 2/12     |        |         |                 |                 |                 |        | 60, begun                           |
| 2/27     |        |         |                 |                 |                 |        | Stopped                             |
| 3/8      | 170    | 5.16    | 84              | 46              |                 | +10    | 100, begun                          |
| 5/21     |        |         |                 |                 |                 |        | Stopped                             |
| 5/24     |        |         |                 |                 |                 |        | 25, begun 3X/wk.                    |
| 7/12     |        | 5.50    | 91              | 49              |                 |        |                                     |
| 9/13     |        |         |                 |                 |                 |        | 50, begun, 3X/wk.                   |
| 9/27     | 173    | 5.58    | 97              | 50              | 6100            |        | Stopped                             |

treatment directed toward the anemia had been employed.

Here as in other cases there was no shift in leukocyte count parallel to that seen in erythrocyte count and the weight tended to be higher during intensive androgen therapy and to increase with the blood count.

Case 4 (table 3) showed a well-marked rise and fall of both the metabolic rate and blood count in response to testosterone propionate, but the determinations

are too few to be significant unless considered in conjunction with the changes in the preceding cases. Methyl testosterone had a similar effect, more marked in the B.M.R. curve. The determinations during early 1941 show a rise in the basal metabolism in response to resumption of methyl testosterone in smaller interrupted doses. An explanation of the lower blood count in the determination in March, 1941, is not obvious. It probably represents a fall toward average normal levels occurring gradually

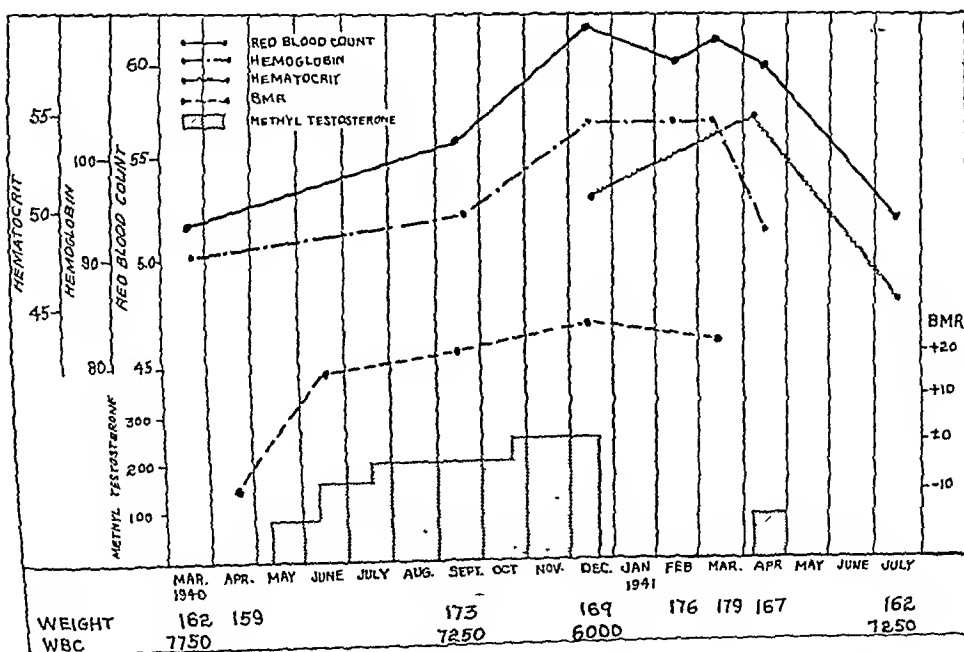


Fig. 2. EFFECT OF METHYL TESTOSTERONE ON BLOOD COUNT OF EUNUCHOID, CASE 5, AGE 21.

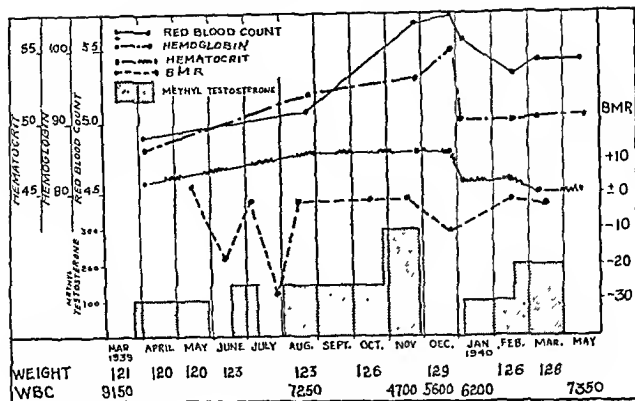


Fig. 3. EFFECT OF METHYL TESTOSTERONE ON BLOOD COUNT OF EUNUCHOID, case 6, AGE 24.

after abandoning the very high doses of October, 1940, and earlier.

Case 5 (fig. 2) was a case of marked eunuchoidism of unknown origin without clinical or roentgenologic evidence of pituitary tumor. The well-defined response of the metabolic rate and blood counts to methyl testosterone therapy are shown. Here as in the other cases there is a rise in body weight paralleling that of erythrocyte numbers, and no significant shift in the number of leukocytes.

Case 6 (fig. 3). This is a case of moderately marked hypogonadism with no clearly defined cause and without clinical or roentgenologic evidence of pituitary tumor. He showed a well-defined response of the metabolism and blood counts to methyl testosterone therapy. On withdrawal of therapy in late November, 1940, the fall of blood count lagged behind that of B.M.R.; the basal rate fell within four weeks after the withdrawal of therapy, but the blood count did

not fall until six weeks after withdrawal.

Case 7 (table 4). This man showed distinct evidence of hypogonadism. His nutrition was good; he lacked the relative pallor seen in the preceding cases; his body contour was relatively normal; his bone age was 17 years. Although both blood count and B.M.R. were not abnormal before treatment, both rose definitely during treatment. When his treatment was changed from methyl testosterone to testosterone propionate for two months, no shift in blood count or metabolic rate was seen.

Case 8 (table 5). Here the evidence of eunuchoidism was present without an accompanying anemia; no change in blood count occurred despite a definite change in B.M.R. in response to institution and withdrawal of methyl testosterone therapy. The dose was smaller than that in most of the other patients, but sufficient to produce rapid sexual maturation.

TABLE 4. Case 7, EUNUCHOID, AGE 24

| Date     | Weight | R.B.C.  | Hemo-<br>globin | Hemato-<br>crit | Leuco-<br>cytes | B M.R. | Therapy<br>Test. Prop. | Methyl Test. |
|----------|--------|---------|-----------------|-----------------|-----------------|--------|------------------------|--------------|
|          | lb.    | million | %               | cc./100 cc.     |                 | %      | mg. per day            |              |
| 10/22/40 | 168    | 5.00    | 91              | 42              | 5200            |        | 100, begun             |              |
| 11/ 9    |        | 4.70    | 84              | 43              | 7400            |        | Stopped                |              |
| 11/18    | 177    |         |                 |                 |                 | -10    | 70, begun              |              |
| 12/23    | 183    |         |                 |                 |                 | +11    | 60, begun              |              |
| 1/13/41  | 186    | 5.90    | 300             | 50              | 5200            | +10    | 12.5                   |              |
| 2/10     | 187    | 5.80    | 94              | 48              |                 |        |                        |              |
| 3/ 8     | 183    | 5.80    | 94              | 48              |                 | + 9    | Stopped                |              |
| 3/31     | 177    | 5.70    | 94              | 48              |                 | + 6    |                        | 60, begun    |
| 5/12     | 186    | 5.60    | 91              | 50              | 1000            | + 9    |                        |              |
| 7/ 7     | 184    | 5.88    | 100             | 52              |                 | +24    |                        |              |
| 7/21     |        | 5.60    | 94              | 51              | 8700            |        |                        | 100, begun   |
| 9/ 8     | 196    | 5.90    | 97              | 52              | 8300            | +37    |                        | Stopped      |
| 9/23     | 181    |         |                 |                 |                 | - 1    |                        |              |

TABLE 5. Case 8, EUNUCHOID, AGED 19

| Date     | Weight | R.B.C.  | Hemo-<br>globin | Hemato-<br>crit | Leuco-<br>cytes | B.M.R. | Therapy<br>Testosterone Propionate |
|----------|--------|---------|-----------------|-----------------|-----------------|--------|------------------------------------|
|          | lb.    | million | %               | cc./100 cc.     |                 | %      | mg. per day                        |
| 10/ 9/40 | 145    | 5.15    | 97              | 44              | 4600            | -15    | 100, begun                         |
| 10/25    | 153    |         |                 |                 |                 | - 5    |                                    |
| 11/ 6    |        |         |                 |                 |                 |        | Stopped                            |
| 11/22    | 157    |         |                 |                 |                 | -13    | 100, begun                         |
| 12/16    | 159    | 5.04    | 94              | 46              | 4350            | + 4    |                                    |
| 1/24     | 167    | 5.14    | 94              | 46              |                 | + 1    | 50, begun                          |
| 3/ 5     |        |         |                 |                 |                 |        | Stopped                            |
| 3/26     | 162    | 5.08    | 91              | 46              |                 | -12    |                                    |
| 4/ 1     |        |         |                 |                 |                 |        | 100, begun                         |
| 6/30     | 163    | 5.19    | 87              | 46              |                 | - 5    |                                    |

### Hypogonadism of Pituitary Origin

Case 9 (table 6) was a pituitary dwarf and was growing rapidly in height during the period of methyl testosterone therapy, although he had grown very slowly previous to its use. A rise in blood count occurred following the use of methyl testosterone; however, the changes of erythrocytes, hemoglobin and hematocrit were not parallel, and thus appeared to reduce the significance of these changes, especially since no hematocrit level was obtained in 1939. The appearance of the patient himself, however, changed considerably during the treatment. In the beginning he had a sallow pallor such as is often seen in cases of pituitary deficiency, whereas after treatment his color was that of a healthy male and his ears which were previously rather white have become noticeably red. The B.M.R. appeared to show some rise on August 26, 1940 but this was not consistent, and on continued large doses was still minus 4 per cent on November 27, an insignificant change as compared to pre-treatment levels. Subsequent continuation of large doses failed to produce hypermetabolism. It can

be seen that the low body weight of this patient indicates a much larger relative dose of androgens than was given in any of the other cases.

Case 10 (table 7). This case was one in which there was roentgenologic evidence of pituitary tumor without visible signs of optic nerve degeneration or visual field defect. He had the body contour of a eunuchoid but was of normal height. A rise in B.M.R. following the use of methyl testosterone was shown on one occasion but the shift in blood count is insignificant. No rise in hemoglobin levels occurred during two and one half months of methyl testosterone therapy.

It is interesting in these two cases of pituitary disease to speculate as to whether the pituitary insufficiency presumed to exist may have been a barrier to the production of such metabolic increases as have been seen in the other hypogonadal patients.

### Patients without Hypogonadism

Of the two sexually mature cases, case 11 (table 8) showed some rise in blood count which is not great enough to be significant, with a well-marked rise in

TABLE 6. Case 9, PITUITARY DWARF, AGE 20

| Date    | Weight | R.B.C.  | Hemo-<br>globin | Hemato-<br>crit | Leuco-<br>cytes | B.M.R. | Therapy<br>Methyl Testosterone |
|---------|--------|---------|-----------------|-----------------|-----------------|--------|--------------------------------|
|         | lb.    | million | %               | cc./100 cc.     |                 | %      | mg. per day<br>(Antophysin)    |
| 4/18/39 | 65     | 4.45    | 78              |                 | 7200            | - 9    | 50, begun                      |
| 2/ 5/40 |        |         |                 |                 |                 |        | 100, begun                     |
| 3/ 6    |        |         |                 |                 |                 |        | 200, begun                     |
| 5/22    | 78     |         |                 |                 |                 | - 9    | Stopped                        |
| 8/26    | 80     | 4.80    | 84              | 42              | 5700            | + 5    | 200, begun                     |
| 9/20    | 76     | 5.00    | 91              | 41              | 6300            | -11    | 300, begun                     |
| 10/14   |        |         |                 |                 |                 |        | Stopped                        |
| 11/27   | 82     | 5.07    | 87              | 43              | 5850            | - 4    |                                |
| 1/11/41 | 79     | 5.10    | 87              | 43              | 6950            | -11    | 60, begun                      |
| 2/ 1    |        |         |                 |                 |                 |        | 200, begun                     |
| 3/ 6    |        | 5.16    | 84              | 44              |                 | - 9    |                                |
| 5/19    | 89     |         |                 |                 |                 |        |                                |
| 6/11    |        | 5.10    | 81              | 44              | 7400            |        | 100, begun                     |
| 6/16    |        |         |                 |                 |                 |        | Stopped                        |
| 6/22    |        |         |                 |                 |                 |        | 200, begun                     |
| 6/27    |        |         |                 |                 |                 |        |                                |
| 10/25   |        | 5.37    | 91              | 46              | 7450            | - 1    |                                |
| 10/31   | 91     |         |                 |                 |                 |        |                                |

TABLE 7 Case 10, EUNUCHOID WITH PITUITARY TUMOR, AGED 20

| Date     | R B C   | Hemo<br>globin | Hemato<br>crit | Leuco<br>cytes | B M R | Therapy              |             |
|----------|---------|----------------|----------------|----------------|-------|----------------------|-------------|
|          |         |                |                |                |       | Test Prop            | Methyl Test |
|          | million | %              | cc /100 cc     |                | %     | mg per day           |             |
| 10/29/40 | 4 18    | 78             | 37             | 3150           | - 7   |                      |             |
| 2/ 1/41  | 4 30    | 78             | 38             |                | -11   |                      |             |
| 2/ 8     |         |                |                |                |       |                      |             |
| 2/13     |         |                |                |                |       |                      | 100, begun  |
| 3/ 1     | 4 30    | 78             | 38             |                | - 5   |                      | 200, begun  |
| 3/14     | 4 45    | 78             | 41             |                | +7    |                      |             |
| 4/ 9     | 4 56    | 78             | 38             | 4600           | +22   |                      |             |
| 5/ 5     |         |                |                |                |       |                      | Stopped     |
| 5/13     |         |                |                |                | - 4   |                      |             |
| 5/24     | 4 53    | 78             | 41             | 4250           |       |                      |             |
| 5/31     |         |                |                |                |       | 50 begun             |             |
| 7/ 9     |         |                |                |                |       | Stopped <sup>1</sup> |             |
| 7/17     |         |                |                |                |       |                      | 200, begun  |
| 8/30     |         |                |                |                |       |                      | Stopped     |
| 9/3      |         |                |                |                |       |                      | 100, begun  |

<sup>1</sup> See note of 7/2 and 7/1

B M R when methyl testosterone was given Case 12 (table 9) whose blood count was originally quite high, showed no definite change in blood count in response to these steroids. Whether such an effect is produced by direct action of the androgens or is mediated by other organs, such as the pituitary for example, is not

TABLE 8 ARTERIAL HYPERTENSION, Case 11, AGED 62

| Date    | Weight | R B C   | Hemo<br>globin | Hemato<br>crit | Leuco<br>cytes | B M R | Therapy                  |                     |
|---------|--------|---------|----------------|----------------|----------------|-------|--------------------------|---------------------|
|         |        |         |                |                |                |       | Test Prop                | Methyl Testosterone |
|         | lb     | million | %              | cc /100 cc     |                | %     | mg per day<br>(bed rest) |                     |
| 8/20/40 |        | 4 3     | 84             |                | 9100           |       |                          |                     |
| 9/20    |        | 4 5     | 81             | 40             | 4250           | -18   |                          |                     |
| 9/25    | 159    |         |                |                |                | -18   |                          | 100, begun          |
| 10/2    | 159    |         |                |                |                | -18   |                          | 250 begun           |
| 10/ 7   | 161    | 4 8     | 87             | 42             | 7450           | - 2   |                          |                     |
| 10/12   |        |         |                |                |                | - 1   |                          |                     |

to therapy although a distinct rise in basal metabolism occurred

## DISCUSSION

Concerning the mechanism by which the sex difference in blood counts is brought about, several

known (b) The greater quantity of androgens in the male may have a direct effect upon the blood forming organs (c) The difference might be due in some degree to genetic factors (d) In the female, menstrual blood loss forms an additional factor in producing lower blood counts

TABLE 9 Case 12, NORMAL SUBJECT, AGED 32 IN JUNE 1941

| Date     | Weight | R B C   | Hemo<br>globin | Hemato<br>crit | Leuco<br>cytes | B M R | Therapy    |             |
|----------|--------|---------|----------------|----------------|----------------|-------|------------|-------------|
|          |        |         |                |                |                |       | Test Prop  | Methyl Test |
|          | lb     | million |                | cc /100 cc     |                | %     | mg per day |             |
| 11/20/40 | 153    | 6 14    | 111            | 56             | 9500           | - 9   |            |             |
| 12/15    | 152    |         |                |                |                | -13   | 50 begun   |             |
| 2/26/41  |        | 6 22    | 108            | 55             |                |       | Stopped    |             |
| 3/19     | 156    | 6 38    | 108            | 55             | 9850           | - 5   |            | 100, begun  |
| 3/24     |        |         |                |                |                |       |            | 200, begun  |
| 4/ 8     | 161    |         |                |                |                | -10   |            |             |
| 5/15     | 165    |         |                |                |                | +17   |            |             |
| 5/28     | 163    | 6 10    |                | 52             | 100            | + 2   |            | Stopped     |
| 8/29     | 157    | 6 01    |                | 53             | 104            |       |            |             |

possible factors may be considered, among which are the following (a) The effect of androgens upon the blood count may be related to the increase in metabolic rate (3-6) which is known to be produced by

Menstrual blood loss is at most only a partial cause of the sex difference in blood counts, since this difference exists between man and postmenopausal women. Also, this difference is well marked in birds

(7, 8). The fact that such a difference exists in both homozygous and heterozygous species argues against the genetic factor.

*Shift in blood count during adolescence.* That a distinct shift in blood count does occur during adolescence has been clearly shown by Williamson (9) in a study of hemoglobin levels in 919 individuals of all ages. He found a rise of about 1 gm. in hemoglobin level in both sexes in his 11 to 16-age-group. Such a rise was shown for hemoglobin, and for erythrocytes as well, in the same age group by Osgood and Baker (10). Williamson noted the first definite sex difference in hemoglobin levels in the 16 to 20-age-group, this difference continuing to the sixth decade.

*Adolescent changes in production of 17-ketosteroids.* The recently published study of Nathanson et al. shows that the urinary excretion of 17-ketosteroids is slightly greater in the male from the ages of 4 to 8 years. A sharp rise occurs in the male from the ages of 8 to 12 and an equally sharp rise of shorter duration in the female, from 9 to 11 years. The sex difference is well-marked after the age of 12, the average output in the female being 75 per cent of that of the male. It appears, therefore, that since a shift in the sex difference in both blood count and 17-ketosteroid production occurs at the same time of life, a causal relationship may exist.

The fact that injections of testosterone propionate or orally administered methyl testosterone raise the basal metabolic rate seems well established. Kenyon (3) found marked increases in cases of eunuchoidism treated with testosterone propionate over a period of months amounting to as much as 38 per cent increase. Thompson and Heckel (4) have reported a similar increase in a case of eunuchoidism. Rossmiller and I (5) reported ten cases of male hypogonadism treated with methyl testosterone showing increases in basal metabolism. The maximum rise in this group was 54 per cent; the average of maximum rises in the ten cases was 27.6 per cent.

*Adolescent changes in B.M.R.* Since it is known that there is a greater increase in 17-ketosteroid production in the male than the female following puberty and since it is known that some of the ketosteroids have the power to raise the basal metabolic rate, it would appear that some sex difference in B.M.R. could be correlated also with adolescence. Such a correlation however, does not appear to have been established and the literature contains some disagreement on this point.

Aub and DuBois (13) found an upward swing in the metabolic rate for prepuberal and puberal males at 12 years, the curve resuming its previous downward course at 14 years. In the data of Boothby and Sandiford (2) and Boothby, Dunn and Berkson (14) the sex difference in B.M.R. is greatest about the age

of 18 years. This difference does not appear by their tables to be significantly greater, however, in adults than in children.

*Relation of B.M.R. to the rise in blood count under androgen therapy.* It is interesting that throughout these studies in those cases in which a blood count response was present, an increase in basal metabolism was also observed. In cases 8 and 11 there was an increase in B.M.R. but no significant shift in blood count. Methyl testosterone in the doses used caused higher levels of the metabolic rate than followed the use of testosterone propionate and for the most part the highest points of metabolic rate in each case were associated with the highest blood counts.

In the three hypogonadal cases in which a response in blood count was least apparent (cases 8, 9 and 10), the rise in B.M.R. was less marked than in the others, the one high level shown in case 10 being an exception. The average maximum increase in basal rate in the cases with a significant response in blood count approximated 38 per cent, while the average maximum increase in the cases which did not show a blood count response approximated only 22 per cent.

The question arises as to whether the rise in basal metabolic rate creates a demand upon the blood for greater oxygen carrying capacity which might result in an increased number of erythrocytes. In some of our data (case 5, fig. 2) the findings suggest that the basal metabolic rate increase precedes the rise in blood count, and in case 6 (fig. 3) there is a fall in metabolic rate which precedes that of blood count. More extensive frequent observations are needed before conclusions are warranted on this point.

The rise in basal metabolic rate caused by androgens has been shown to be intimately connected with other metabolic shifts. Among them is a retention of protein (12, 15, 16). Under proper circumstances androgens also stimulate growth of new tissue, not only of the genitalia but also of skeletal muscle as well (17, 18). It appears likely that such a set of factors favoring growth may also facilitate the formation of blood cells.

The existence of anemia is not necessary for the demonstration of this effect, nor does the presence of a normal blood count in itself necessarily preclude the production of such a change. Case 5 (fig. 2) and case 7 had normal counts before therapy was begun and yet showed a striking response.

In the eight cases of hypogonadism reported here which had no obvious evidence of pituitary disease, the blood count was raised by methyl testosterone or testosterone propionate in seven. It may be of importance that the rise in blood count in the two patients in whom pituitary disease was present was relatively slight or insignificant. This suggests the possibility that pituitary hypofunction in some way

forms a barrier to as full a metabolic response to androgens as may otherwise occur.

The fact that body weight increases at the same time as the erythrocyte count does so, as well as the fact that there is no accompanying shift in leukocyte count, both attest to the fact that there is an actual increase in the number of red cells in circulation and that the findings are not the result of hemoconcentration. Whatever the actual mechanism of such a shift in blood count may be, these data suggest that the rise in blood count and possibly that of the metabolic rate as well may be a reproduction of changes observed in normal individuals during adolescence.

Such findings support the view that sex differences in blood count are hormonal and metabolic, not genetic in nature. In this sense the higher red cell count of the male may be considered a secondary sexual characteristic. It appears probable that excessive quantities of adrenal cortical steroids produce the increased erythrocyte counts seen in cases of Cushing's syndrome, adrenogenital syndrome and adrenal cortical tumor by a similar mechanism.

The striking effect of androgens in raising the blood counts in cases of hypogonadism is apparent. The blood counts have increased from anemia levels to high normal in some instances. Such distinct changes as these bring to mind the possibility that androgens may be useful in the treatment of certain cases of anemia in which hypogonadism is not as apparent as in these cases.

#### SUMMARY AND CONCLUSIONS

Twelve individuals were treated with testosterone propionate, methyl testosterone, or both. Eight were eunuchoids without evidence of pituitary disease, two had hypogonadism with evidence of pituitary disorder, and two were sexually mature men.

Observations on the erythrocyte, hemoglobin, hematocrit and leukocyte levels of the circulatory blood were made over periods varying from 1 month to 8 years. Active treatment extended over more than 4 years in some cases.

In 7 of the 8 eunuchoid patients without pituitary disease, there was a rise in erythrocyte, hemoglobin and hematocrit levels with therapy or a fall on withdrawal of therapy, or both. In the others, the response was insignificant or absent.

Those patients showing a rise in blood count also showed a rise in B.M.R. which approximately paralleled it. An increase in metabolic rate occurred with treatment in the other cases, but on the whole it was less marked, and with a single exception (case 10) did not rise significantly above normal range.

These findings suggest that the changes in erythrocyte and hemoglobin levels observed with androgen therapy are related to changes in the basal metabolism and perhaps other intimately connected metabolic shifts. We believe we have reproduced a rapid form of change in the hematopoietic system which occurs more slowly in normal individuals during adolescence.

Attention is directed to the possible value of androgens in the treatment of certain cases of anemia.

We are grateful to Miss Irene Smith for valuable technical assistance.

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# Gonadotropic Hormone: Modification of the Alcohol- Precipitation Assay Method

## [[Gonadotropin Assay]]

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WITH THE ACCUMULATION of experience in the concentration and purification of the gonadotropic hormones isolated from the urine of normal (1, 2, 3) and endocrinological patients, a gradual evolution of the technical procedure (4) has taken place. The evolution has proceeded in the direction of reducing toxicity of the concentrate and increasing the simplicity and ease of preparing the concentrate.

The urine collections are made during a 12-hour overnight period, usually from 7 P.M. to 7 A.M. The specimens are kept in a refrigerator, without added preservative, until precipitated. Male patients are requested to collect four successive separate specimens. All are precipitated but only one specimen is assayed. If the assay results are high or normal, the remaining specimens are then completely concentrated and assayed separately to confirm the findings of the first. If the assay results are low, the remaining three specimens are pooled and the combined concentrate assayed in a single animal. Female patients are instructed to begin collections five days prior to their next anticipated menses. Often this necessitates collecting more than five specimens because of miscalculation. Only the last five are used. These are combined and a one-day aliquot is concentrated and assayed. If the assay results are low, a similar 2 or 3-day aliquot may be assayed. Otherwise the first assay is checked by further similar assays.

The five-day period preceding the next menses is chosen because of the greater likelihood of avoiding the main peaks of excretion of the menstrual cycle (3). Any peak which might occur during this period is minimized by the pooling process and thus a fair estimate of average function is attained.

All cloudy urine is filtered through soft filter paper to remove precipitated salts, mucin, and other debris. The entire 12-hour urine specimen is then precipitated

with 4 to 6 volumes of 95 per cent ethyl alcohol and permitted to settle overnight or longer. One gallon, wide-mouth, glass jars are suitable for precipitation. The alcohol-precipitated urine may stand in a refrigerator or cold room for months without appreciable loss of potency. The clear supernatant fluid is siphoned off and the residual precipitate is centrifuged 4 to 5 minutes in a 250 cc. centrifuge tube. The precipitate is washed twice with ethyl ether, centrifuging off the ether each time. Both the original wide-mouth container and tube are dried before a fan and the dried precipitate is transferred into an osmosis cellophane dialyzing bag.<sup>1</sup> Repeated tap water rinsings are made of both containers until all the precipitate has been transferred to the dialyzing bag. As much as 100 to 150 cc. of water may be used to effect the transfer. Smaller amounts of water offer no advantage since the volume often rises to this level during dialysis. The contents are dialyzed against cold running tap water overnight.

This procedure accomplishes original concentration of the protein hormone, elimination of the alcohol, fat-soluble substances, and especially steroids. The dialysis eliminates electrolytes and other molecules of low molecular weight. This step is highly important when large amounts of urine are being concentrated for injection into a single animal because the toxic substances (mostly salts) are dialyzed out. This is apparent in the lower fatality rate, and rarity of constitutional symptoms and local reactions, such as the matted skin and subcutaneous tissue about the injection site. Despite the foregoing precautions an occasional animal will die. The elimination of electrolytes during the 12-hour dialysis process has another advantage in that the protein hormones become more completely soluble as the amount of salt decreases.

After dialysis, the entire contents of the bag are returned to the original unwashed 250 cc. centrifuge

<sup>1</sup> C.E.N.C.O. No. 70160A. Tubing 1 1/8 inches in width and 0.00072 inches thick.

tute and after the rinsings are added, the precipitate is centrifuged down. The supernatant liquid is poured off into beakers and reprecipitated with 4 to 6 volumes of 95 per cent ethyl alcohol, and the precipitate is permitted to settle overnight. Difficulty is occasionally encountered in causing the protein hormones to reprecipitate. A number of measures may be taken to obviate this difficulty, including vigorous stirring or shaking, increasing the concentration of alcohol, adding 0.5 mg of NaCl, and adding 5 to 10 cc of ethyl ether.

The clear supernatant liquid is siphoned off and the residue transferred to pointed tip 50 cc centrifuge tubes and centrifuged for 2 to 3 minutes. The precipitate is thoroughly mixed with ethyl ether and centrifuged again before it is dried in front of a fan, along with the precipitating beaker. This last step is virtually the same as the earlier washing and centrifuging of the first precipitation since here again the beaker is retained to be washed. It can also be used to hold the washings of the syringe.

The small dried cake of precipitate is most conveniently broken up with an 18 gauge, 2 inch needle attached to a 5 cc syringe. Neutral distilled or tap water is flushed through the precipitating beaker with the syringe three separate times and added to the precipitate in the centrifuge tube three separate times, centrifuging off the final solution for use each time. The water is added in 3, 1½, and 1½ cc amounts to both the beaker and centrifuge tube. The precipitate is completely broken up and exposed to the water by repeatedly drawing it up into the syringe and forcefully expelling it. The solution of hormone, now in the form for injection, is contained in a total volume

of 6 cc so that 1 cc injections can be made twice daily for three successive days. If cloudiness or precipitates remain in the final injection solution, a further centrifuging of the whole amount before injection may eliminate this. Assay rats are 22 to 24 days old at the time of the first injection and are killed by rapid decapitation 14 to 16 hours after the final injection. Vaginal opening, although somewhat capricious for use as an assay end point, is noted at autopsy. The uterus and ovaries are dissected free and weighed separately (preferably on a Roller Smith torsion balance) as previously described (5).

Results, using the above simplified procedure, have been more uniform, and slightly higher than with the use of previously described methods.

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#### ADDENDA

- R. F. Varney and F. C. Koch, reporting in *Endocrinology* 30: 399, March, 1942, suggest that dialysis causes marked reduction

in variations in the cellophane osmosis membranes used. One notes that deaths occurred in many of their assay animals regardless of the extraction method used. The extracts prepared by the alcohol dialysis-alcohol precipitation method have, in our experience, caused death in less than one per cent of the animals.





# The Effect of Pregnant Mare Serum Hormone on a Case of Primary Hypo-ovarianism

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## [Ovary and Gonadotropin]

THE FOLLOWING CASE of primary hypo-ovarianism is presented because of its typical signs and symptoms and to demonstrate the production by treatment of the physiological phenomena of a normally approaching puberty.

### CASE REPORT

G.P., age 15 years and 9 months, was first seen at the Greenpoint Hospital Out-Patient Clinic on April 6, 1940.

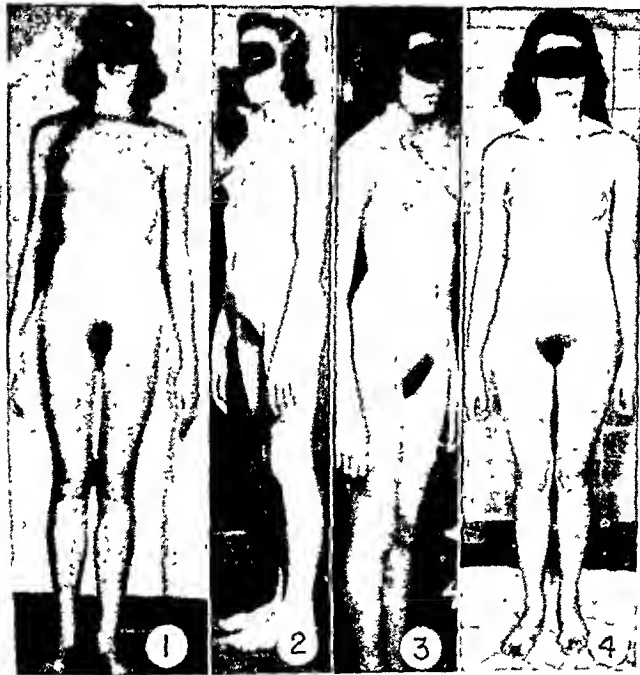


Fig. 1. G.P., age, 15 years and 9 months; before treatment, 4/6/40. Fig. 2. After treatment was discontinued 10/24/40. Fig. 3. Three months later, 2/28/41. Fig. 4. One year later, 2/18/42.

The fact that she had grown 5 inches in height during the preceding year was the chief complaint made by her mother. Besides not having menstruated as yet, headaches, frequent colds, and constipation associated with cramps, completed the story of accompanying symptoms.

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She was a full-term baby, weighing 10 pounds at birth, and she developed normally. Pubic hair and a slight bulge about the mamilla had appeared at fourteen and one-half years. These have not increased in amount or size during the last year. Headaches over the right side of the head occur frequently. She is agreeable and helpful at home but shows no sign of sociability; nor does she take any interest in outside activities. Her school work is just passable.

The maternal grandmother and paternal grandfather were obese; her father is tall and stout; her mother tends towards obesity and is of a neurotic disposition; one brother, older, is apparently normal.

*Examination.* G.P. is a tall, thin and pale girl. One is struck at once by her eunuchoid proportions, her juvenile visage, and her quiet and reserved demeanor. Although she co-operates perfectly and is agreeable to all routine requirements, a definite shut-in personality with an absence of normal aggressiveness is evident.

The skin is pale with no blemishes. There is no axillary hair; the pubic hair is scant; the escutcheon, normal. Decreased somatic development is apparent in her long, thin frame (figure 1). The small mammary bulge is soft and insensitive. The abdomen is thin and flat. Teeth are rather well-spaced; dentition moderate. The heart and lungs are normal. The external genitalia appear hypoplastic and dry; no internal examination was made.

The body weight is 108 pounds; the height, 64½ inches; span, 68 inches; lower measurement, 34 inches.

The B.M.R. is normal; the blood count relatively normal; hemoglobin, 75 per cent. The roentgenogram revealed the olecranon epiphysis to be partially united; the metacarpal and phalangeal epiphyses show no sign of union. The bone age is about 13 years (1, 2).

The vaginal smears are dry, the material is scant and obtained with difficulty. When stained with crystal violet the smears reveal thick clumps of material containing a few well-defined cells, many of which are from the deep layers, and very little debris. The picture microscopically is one of well-advanced atrophy of the vaginal epithelium (fig. 5).

*Summary of findings.* There is an absence of the menarche; a delay and absence of progressing development of secondary sexual characteristics; an overgrowth of the long bones producing eunuchoid proportions; a delayed union of the epiphyses; poor somatic development; juve-

nile mannerisms and psyche, an absence of signs and symptoms pointing to the thyroid or pituitary glands as possible causes for the ovarian deficiency. These signs, varying in degree only, are cardinal and comprise the diagnosis and differential diagnosis of primary hypovarianism (1, 2).

**Treatment** Treatment was begun on May 6, 1940. Intramuscular injections of pregnant mare-serum hormone, 400 international units<sup>1</sup> were given daily for 12 days beginning every 28th day. Thyroid extract, 1 grain daily was prescribed. Vaginal smears were taken every other day.

**Results of therapy** Towards the end of June, after the second course of treatment, the mammary glands showed signs of resuming growth. At the same time the vaginal smears became more moist, the clumps of cells less compact, the individual cells more discrete, and changed from oval to a pentangular form, deep cells were numerous. During the next month evidence of proliferation of the vaginal mucosa could be found in the appearance of large, well defined cells, a diminution of the number of deep cells, and a normal amount of bacteria and leucocytes. From that point on, improvement in the appearance of the vaginal smears took place in a sequence not unlike that seen in the smears of menopausal women receiving estrogenic therapy (3). On Aug. 30, 1940, the smear contained uniformly large cells and a few leucocytes. Two days later the smear contained typical cornified cells only. Within 24 hours bacteria and leucocytes appeared in large numbers, the cells became elongated and the nuclei were large. Within the last week prior to menarche the character of the smears changed rapidly and they resembled closely those observed in the premenstruum of normal women. In a broad sense a comparison of the vaginal smears in this case may be made with those of prepubertal girls as they approach normal puberty (4). In the latter instances, however, the process is slower and demonstrable only over a longer period of time.

Although at no time during treatment with gonadotropin was estrogen given, the vaginal smears became clearer and cleaner as bacteria and leucocytes gradually diminished in amount until on Aug. 30, 1940 (fig. 8), after the fifth course of treatment, there appeared a vaginal smear containing typical cornified cells (5). The menarche occurred on Sept. 10, 1940, lasted 7 days and was accompanied by no discomfort. All treatment was discontinued at this time (fig. 2).

By Feb. 28, 1941, no further excessive linear growth had occurred and the olecranon epiphyses were completely united, the epiphyses of the hand were partially united, the menses had recurred normally and regularly to date, the secondary sexual characteristics continue to show improvement (fig. 3).

On Feb. 18, 1942 the growth recorded since treatment was started is  $\frac{3}{8}$  inch, the hand epiphyses are completely united, the menses appear normal and regularly. In every way the patient has developed into an apparently normal

young woman. The eunuchoid proportions naturally remain (fig. 4).

#### DISCUSSION

We have been dealing with a condition, all symptoms of which can be attributed to the absence of estrogenic hormones (6, 7, 8). The processes of maturation resulting in puberty are synchronized culminations of physical and physiological interrelationships (6-11). In order for the ovary to play its part properly in these reactions, it must produce estrogen, not only for its effect on the genital and somatic systems, but also for its effect on the other ductless glands (6, 8). To accomplish this effectively its development must be completed according to a physiological schedule.

It is believed at present that the ovary at birth is composed of a large cortex which contains primordial follicles. Deep in the medulla, primary follicles containing the definitive germ cells attempt to develop but, their span of existence being short, they soon undergo atresia or cyst formation (11, 12). In the next 12 to 14 years, the entire cortex disappears, while the follicles in the medulla survive for longer periods and gradually succeed in producing some estrogen before being inactivated (6). The cumulative result of this prepubertal follicular activity produces the estrogen responsible for the secondary sexual characteristics and prepares the genital tract for puberty. Finally, when the entire original cortex has disappeared, the large follicles near the surface of the ovary can rupture and liberate their ova. Thus, in the ovary itself, there are morphological changes which must also be completed according to schedule since, no matter how large the follicle, or how great the amount of estrogenic hormone produced, unless the infantile cortex disappears, rupture of the follicle through the surface of the ovary to release the ovum is impossible. A delay in rupture necessarily results in death of the ovum, little or no luteinization, and above all, little chance for normal rhythmic ovarian physiology (6, 7, 11, 12).

In primary hypovarianism, in which no other glands seem to be responsible for the gonadal insufficiency, it has been assumed that the gonads themselves are refractive to gonadotropic stimulation (1, 2). But this apparent refractiveness may well be an inability to respond on the part of an ovary whose development is so much retarded as to make it appear that all function has ceased. Immature ovaries cannot be expected to react to gonadotropic influences as do mature ones, i.e., with follicle rupture, ovulation, and luteinization (6, 7). Refractiveness, therefore, may be an incorrect term. The ovary in question may be actively undergoing histological changes, and may even make up for its retardation under active spurring by an exogenous gonadotropin. Conditions produced by a prenatal unbalance of maternal hormones (12,

<sup>1</sup> The gonadotropic hormone from the serum of pregnant mares (Anteron) was supplied by the Schering Corp., Bloomfield, N. J.

The basal metabolism was minus 8 per cent.

The parents, being disturbed by the genital abnormality of the patient and convinced that she was a female in habits and actions, requested that the penis be removed. This was agreed to and it was further proposed

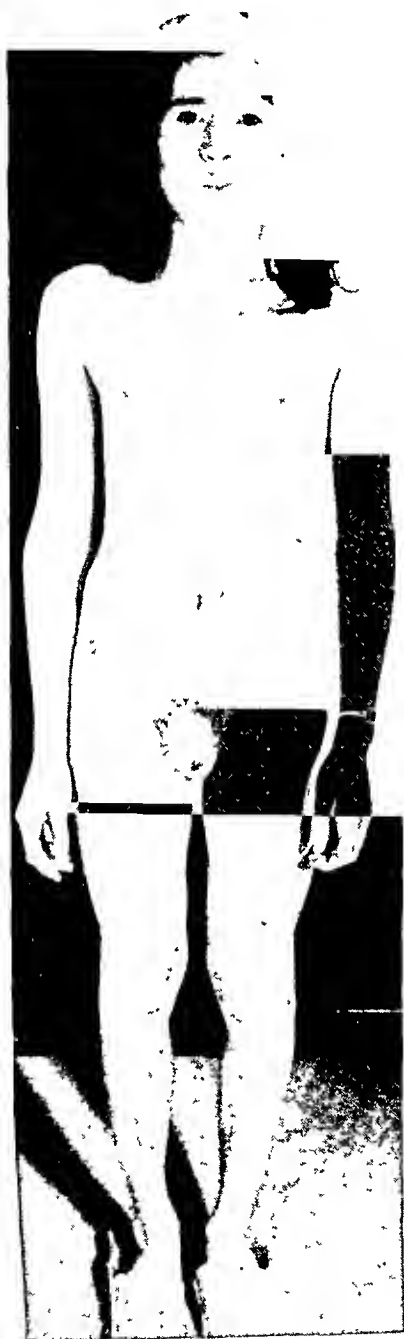


Fig 1. CONFIGURATION OF BODY WITH MALE TYPE BREAST, RUDIMENTARY PENIS.

to do an exploratory laparotomy. Consequently on July 23, Dr. N. Allen performed a 6-inch low median laparotomy. Both adrenal areas were palpated, the surgeon's impression being that there was no abnormal enlargement. The spleen was freely movable. The right lobe of the liver was enlarged.

Examination of the pelvis revealed that a rudimentary uterus (finger-like in shape) approximately 4 cm. long and 2 cm. in diameter was present. It was embedded in tissue resembling the broad ligament. Extending from the uterus were the right and left fallopian tubes with their fimbriated ends. On the right side just beneath the fallopian tube, near its distal end and normally situated was a small but normal-appearing ovary. About 2 inches (5 cm.) from the rudimentary uterus was a testicle, 2 cm. long, bluish-white in color. It was easily removed.

On the left side, in the same relative position as on the right beneath the fallopian tube was a testicle about 2 cm. in diameter, white in color with a shiny capsule. This was removed. There was a definite contrast between the bluish-white color of the right testicle and the white fibrous appearing testicle on the left side. Neither tube nor rudimentary uterus was removed, and the right ovary was also not disturbed. Appendectomy was performed.

Following closure of the laparotomy wound, the patient was put up in stirrups and a catheter inserted into the bladder. The entire penis was removed and a plastic reconstruction was done (fig. 4).

Other than a superficial infection of the abdominal wound which caused a fever for 10 days, her recovery was uneventful.

The pathological report was as follows.

"The penis with a normally formed glans and prepuce, measures 5 cm. No evidence of an orifice. On section two oval shaped brown areas of tissue—corpora cavernosa penis.

There are two rounded slightly flat masses, the right one is 2 cm. long, bluish-white in color and on section show a yellowish-white papilliferous mass apparently not divided by fibrous septae, doughy in consistency. The left mass, pearly white in color, is firm and there is a white mass encapsulated from the surrounding parenchyma."

The microscopic report was. "1. Cavernous tissue.

2. Right testis: malignant teratoma of the seminoma type (fig. 5). The stroma is richly infiltrated with lymphocytes and is composed of large round cells of the embryonal type. There is every indication of a rapid growth of the malignant embryonal element.

Left testis: Epidermoid cyst in hypoplastic testis."

On July 18, a 12-hour specimen of urine totalled 1615 cc. Gonadotropic hormone assay was made according to the method of Heller and Heller (1). Injection into a rat produced a 1+ vaginal opening. The uterine weight was 90 mg. and the ovarian weight was 87.5 mg. The amount of the hormone present was the same as that usually found in castrate or menopausal urine.

On Jan. 10, 1942, approximately 6 months after operation, a 12-hour specimen of urine totalled 2225 cc. The same procedure for gonadotropic hormone assay in the rat produced a negative vaginal opening. The uterine weight in the rat was 21.1 mg. and the ovarian weight was 14.4 mg. This type of assay response would be normal for a 14-year-old girl who had not reached puberty. There is sufficient contrast between the gonadotropic content of the urine in the pre-operative and post-operative periods to be of some significance. However, deductions from single assays cannot be made with any conclusiveness.

## COMMENT

The parents of the child stated that they had not seen anything abnormal about her genitals when she

As a child she played with dolls and acted like a normal female. At the age of 11 she took up sewing and applied nail polish. She attended school at the



Fig 2. RUDIMENTARY PENIS Fig 3. PENIS WITH RAPHE, LATERAL WALLS OF URETHRAL FOLDS FORMING LABIA MINORA. NORMAL APPEARING VAGINAL OPENING. Fig 4. VULVA AFTER REMOVAL OF PENIS AND PLASTIC RECONSTRUCTION

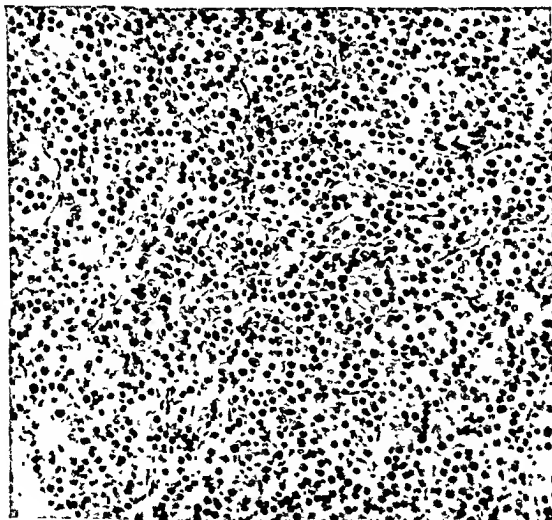


Fig 5. TERATOMA OF THE TESTICLE OF THE SEMINOMA TYPE.

was a baby. Her father had frequently bathed her and did not see any abnormality. The parents and the patient agreed that the voice became masculine three years ago at the age of eleven.

age of 6, did well in her classes, the 9th grade. She never had vaginal discharge. The last the enlargement of the

voice all appeared at about the same time, 3 years ago.

One might assume that the intra-abdominal testis and specifically the active right testis gave off testicular hormone at this time when the patient was nearing puberty. As to when the tumor became actively malignant is of course uncertain.

Young (2), in his treatise on genital abnormalities and hermaphroditism said, "The gonadal anlage may be reversed and hormonal factors also may contribute to the sexual deflection by secretory hormones which have opposite effects than those normally secreted by the developing ovary or testis, as the case may be. What started out to be anatomically an ovary might secrete androgenic substances similar to chemical structures and biological actions to the testis hormones. Hormonal intersexuality is probably a phenomena of later embryonal life just as it sometimes occurs in adults with masculinizing tumors. It is probable, according to Goldschmidt's hypothesis, that most pseudohermaphrodites are on a genetic basis and the chromosomal structure of all their body cells are either the male or female formula. However, the opposite sex determining factors or forces in the individual cells are dominant and much greater, so at some point (drehpunkt) in development they turn the future development into a cell having the opposite sex characteristics." The latter is probably what took place in the patient here reported.

The approach of puberty set the sex mechanism in motion and the dormant testis teratoma became activated so that hermaphroditism then followed. The right testis in contrast to the left testis as the pathological report shows, was no doubt the responsible factor for the hermaphroditism.

Vastola (3) reported in interesting male hermaphrodite, aged 37, with a pelvic tumor. This was revealed on laparotomy to be an embryonal carcinoma of an abdominal testis with a twisted pedicle and hemorrhage into the tumor mass. Dr. James Ewing who examined the specimen stated that it was a large round and polyhedral-cell carcinoma. It was atypical teratoid cancer and of teratoma origin not derived from the tubule cells, as tumors that may possibly originate from tubule cells and may be called seminoma generally are more alveolar in structure and lack lymphoid stroma. Yet Ewing did not insist too strongly on the exact derivation of this particular tumor which impressed him as an embryonal growth.

Carmichael and Oldfield (4) reported a case of male pseudohermaphroditism in a 'girl,' aged 14, with a large intra-abdominal teratoma. The tumor, which arose by a short pedicle from the site of the left ovary, was removed along with the fallopian tube and broad ligament. Its removal revealed an abnormality at the site of the right ovary, there was no ovary proper but

only a small nodule of what appeared to be ovarian tissue in the posterior layer of the broad ligament. The uterus and right tube were small but otherwise normal. The tumor was found to be a 'typical small-cystic teratoma containing numerous derivations of all three germ-layers, some at a primitive embryonic stage of development, others with a fully differentiated adult structure.'

Klaften (5) reported a case of pseudohermaphroditism associated with a large-celled ovarian carcinoma. He discussed the origin of these ovarian tumors which give rise to pseudohermaphroditism. They begin, he said, as a solid tumor of the ovary which was designated for a long time as alveolar sarcoma. Von Werdt called them solid granulosa cell tumors and derived from unused granulosa cell elements. Robert Meyer said that these tumors have all various types of designations. Von Pick termed them 'epithelioma chorio-ectodermale'; Von Krompecher gave them the name 'endothelioma'; Von Werdt 'granulosa cell tumors'; Von Chevassu 'seminome'; Ewing, 'Embryonal carcinoma of the testicle'; Klaften favored R. Meyer's term 'disperminome.'

Ewing (6) in discussing the embryonal tumor of the testis said, "The most frequent tumor of the testis is composed of large round or polyhedral cells of embryonal type, lying diffusely or in large alveoli. The stroma is often richly infiltrated with lymphocytes. Through the demonstration by Wilms, Ohkubo and others, that many of these tumors contain teratoid elements, the suspicion first stated by Langhans, that the tumors are teratoid, has been confirmed. Yet Chevassu, Debornadi, and others derive this tumor from the spermatoblasts or embryonal equivalents, and separate this group from the teratomas with which they are so often associated. Several considerations forced the writer to conclude that this common tumor of the testis is always a one-sided development of a teratoma, and is not derived from the adult spermatoblasts." Ewing then goes on to give these reasons.

#### SUMMARY

A case of hermaphroditism in a girl aged fourteen is reported. A 5 cm. long penis-like structure with a normal appearing glans penis and prepuce was present. A normal-sized vagina, a rudimentary uterus, normal tubes with a right and left sided testis and a right-sided ovary were present. The testis on the right side was a highly malignant teratoma of the seminoma type. The left testis was hypoplastic and contained an epidermoid cyst. The body build was of masculine type as was the voice and hair distribution.

Her inclinations and habits were those of the female sex. Gonadotropic hormone assay before and after

operation reveal a significant difference in that pre-operatively the amount corresponded to that found in the urine of castrate and menopausal women, whereas 6 months post-operatively the amount was normal for a 14-year old girl.

At the present time (February, 1942) she is doing well in school, engages in the usual activities with other girls, goes swimming without embarrassment, does sewing, uses lip rouge and nail polish. She considers herself a normal girl.

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# Effect of the Vitamin B Complex in Diabetes Mellitus<sup>1</sup>

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BECAUSE MEMBERS of the vitamin B complex are concerned in carbohydrate metabolism, it has been suggested that they might have an ameliorating effect in diabetes mellitus. Clinical trials (1) with thiamine hydrochloride have been disappointing, but in experimental diabetes, Chaikoff and Kaplan (2) have shown that the administration of whole vitamin B complex prolongs the life of depancreatized dogs. We have, therefore, tried the vitamin B complex in clinical diabetes, but without benefiting the condition.

## METHODS

Assessing the effect of a therapeutic measure in diabetes is difficult because of the great fluctuations in severity which many patients manifest. Elderly diabetics, in particular, often may take 20 to 30 units of insulin daily less than their true requirement, and only gradually over weeks develop marked glycosuria. The effect of infections is likewise well-known. It is possible that serial glucose tolerance tests would be the most accurate criterion for judging the condition of a diabetic, but such tests were not made in our patients. Patients in two principal categories were used. a). Those who took no insulin but had glycosuria, in whom improvement could be shown by a decrease in the amount of sugar lost in the urine. b). Those taking insulin, who could be rendered sugar-free, or could have their dose of insulin reduced.

Only patients were chosen whose long (months to years) attendance in the Diabetic Clinic had led to more or less constant values for body weight, insulin dosage (doses varied from 0 to 120 u daily) and degree of glycosuria (from none to 3 plus by Benedict's test). The patients were observed at weekly or bi-weekly intervals while taking the vitamin B preparation. During subsequent periods when the vitamin

preparation was withdrawn a placebo resembling the vitamin preparation was given.

The vitamin B complex, a heavy syrup obtained from rice bran, was given in a dose of one ounce daily.<sup>2</sup> This amount contained the following quantities of vitamins: thiamine hydrochloride, 4.5 mg.; riboflavine, 300 micrograms; vitamin B<sub>6</sub>, 4.5 mg.; nicotinic acid, 60 mg.; pantothenic acid, 12 mg.; the filtrate factor (Jukes-Lepkovsky) was 28 per cc.

## RESULTS AND DISCUSSION

Twenty-one patients were given the vitamin B complex for periods of from 3 to 16 weeks, with the results shown in table 1. There was no significant change in weight, glycosuria or insulin requirement. The slight increases or decreases noted were only 1 or 2 pounds of body weight, a change of one plus in the Benedict's reaction, or a change in insulin dosage of 2, or at most 4 units.

Although both insulin and members of the vitamin B complex are involved in carbohydrate metabolism, and may to some extent be supplemental as demonstrated in animal experiments, this summation of action could not be shown in diabetic patients. Many of the patients felt better generally, especially, in that they slept better and their appetites improved. This is to be interpreted as a rectification of an unrecognized deficiency state rather than as amelioration of the diabetes.

## CONCLUSIONS

Large doses of a potent vitamin B complex preparation, given for periods up to 16 weeks to diabetic patients, had no discernible effect on the severity of the disease.

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<sup>1</sup> Assisted in part by the Rockefeller Fluid Research Fund and an Anonymous Fund for the Study of Diabetes of the Stanford University School of Medicine.

<sup>2</sup> The vitamin B complex (Galen "B"), and the placebo used were furnished by the Galen Laboratories of Berkeley, California.

TABLE I. COMPARISON WITH PREVIOUS CONTROL PERIODS

| Patient | Drug <sup>1</sup> | Duration of Medication, Weeks | Insulin Requirement     | Glycosuria                         | Body Weight             | Remarks  |
|---------|-------------------|-------------------------------|-------------------------|------------------------------------|-------------------------|--|
| 1       | B<br>P            | 12<br>2                       | Same<br>Same            | Slight decrease<br>Slight increase | Same<br>Same            | Feels and sleeps better                            |
| 2       | B<br>P            | 12<br>12                      | Same<br>Same            | Same<br>Same                       | Same<br>Same            |  |
| 3       | B<br>P            | 12<br>12                      | Same<br>Same            | Same<br>Same                       | Same<br>Same            | Feels the same                                     |
| 4       | B<br>P<br>N       | 12<br>4<br>6                  | Same<br>Same<br>Same    | Same<br>Same<br>Same               | Same<br>Same<br>Same    | Feels the same<br>Feels the same<br>Feels the same |
| 5       | B<br>N            | 5<br>11                       | Slight decrease<br>Same | Same<br>Same                       | Slight decrease<br>Same | Feels better<br>Feels better                       |
| 6       | B<br>N            | 3<br>12                       | Increased<br>Increased  | Increased<br>Same                  | Same<br>Decreased       | Feels the same<br>Feels the same                   |
| 7       | B<br>P            | 16<br>6                       | Same<br>Same            | Same<br>Same                       | Same<br>Same            | Feels better, appetite better                      |
| 8       | B<br>N            | 12<br>2                       | Slight increase<br>Same | Same<br>Same                       | Same<br>Same            | Feels same, appetite better<br>Appetite better     |
| 9       | B<br>P            | 15<br>4                       | Same<br>Same            | Same<br>Same                       | Same<br>Same            | Feels worse  |
| 10      | B                 | 3                             | Same                    | Same                               | Same                    |  |
| 11      | B<br>P            | 12<br>8                       | Same<br>Slight increase | Same<br>Same                       | Same<br>Same            |  |
| 12      | B                 | 8                             | Same                    | Same                               | Same                    |  |
| 13      | B<br>B            | 16<br>8                       | Same<br>Same            | Same<br>Same                       | Same<br>Slight increase |  |
| 14      | B<br>P            | 4<br>4                        | Same<br>Same            | Same<br>Slight increase            | Same<br>Same            |  |
| 15      | B                 | 16                            | Same                    | Same                               | Slight increase         |  |
| 16      | B                 | 8                             | Slight increase         | Same                               | Same                    | Feels better                                       |
| 17      | B                 | 8                             | Same                    | Same                               | Same                    |  |
| 18      | B<br>P            | 8<br>4                        | Same<br>Same            | Same<br>Same                       | Same<br>Same            |  |
| 19      | B                 | 4                             | Same                    | Same                               | Same                    | Feels the same                                     |
| 20      | B<br>P            | 12<br>8                       | Increased<br>Increased  | Same<br>Same                       | Same<br>Same            |  |
| 21      | B                 | 4                             | Same                    | Slight increase                    | Slight decrease         |  |
| 22      | B<br>P            | 12<br>8                       | Same<br>Same            | Same<br>Same                       | Same<br>Same            |  |

<sup>1</sup> B, vitamin B complex, P, placebo, N, neither vitamin nor placebo



# Repeated Glucose Tolerance Tests in Hyperthyroidism

## [Thyroid and Glucose Tolerance]

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THIS STUDY, based on 131 repeated glucose tolerance tests, performed before and after operation, in fifty cases of hyperthyroidism, constitutes one part of a comprehensive investigation on repeated glucose tolerance tests in children, in adults, and in adults with hyperthyroidism. The results in the first group have already been published (1). The results in the group of adults without hyperthyroidism are now in preparation.

The glucose tolerance tests in all instances were performed on fasting patients. One hundred grams of glucose was administered by mouth in 250 cc. of

compare these findings with those obtained in the other groups of cases, that is, in children (patients less than 20 years of age), and in adults who did not have hyperthyroidism. These comparisons are shown graphically in figure 1. The most striking fact shown by this chart is that patients with hyperthyroidism who displayed a normal glucose tolerance curve at the outset continued to show a normal curve, indicating that the carbohydrate metabolism remained intact, in spite of hyperthyroidism. This 100 per cent incidence of a continued normal curve is much higher than in the adults who did not have hyperthyroidism, and also than in the group of children. Since the incidence of diabetes in patients with hyperthyroidism is greater than the general incidence of diabetes by more than 100 per cent the complete stability of the normal glucose tolerance curve in these patients with hyperthyroidism would suggest that when the carbohydrate metabolism remains normal despite the stress of hyperthyroidism, it must indicate that the individual patient has a good insulogenic reserve.

The stress of hyperthyroidism is temporary, and if it is due to factors other than an effect on the insulogenic apparatus itself, it might be expected that a considerable number of patients who displayed a disturbance of carbohydrate metabolism during the period when the thyroid was hyperactive would show a return to normal when this was eliminated by operation or other means. The data in figure 1 show that this was true in comparison to the group of adults who did not have hyperthyroidism. The percentage of patients with hyperthyroidism whose glucose tolerance curves returned to normal was 38.7 per cent, while in the patients who had no hyperthyroidism, the figure was 29.6 per cent. In the group of children, the percentage that returned to normal was higher than in the hyperthyroid group, 45.5 per cent. But this figure was based on only 19 cases, so the percentage figure may be misleading. If the values for the adults and children are grouped, the average for the two is 31 per cent, which indicates that the return to normal is considerably higher in the hyperthyroid group.

In the three groups of cases we find that in 80.6 per

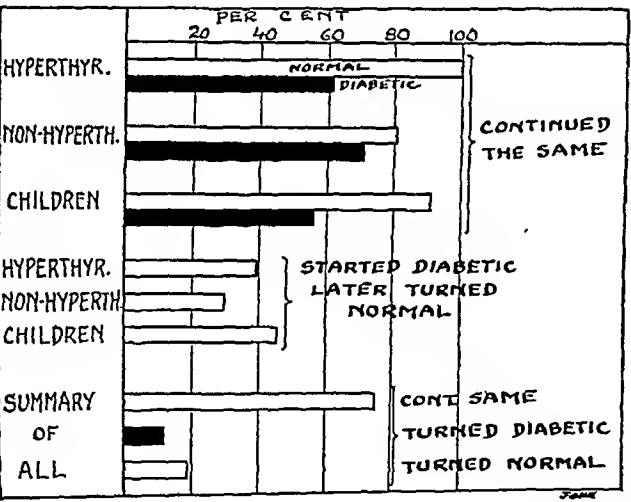


Fig. 1. COMPARISON OF THE RESULTS OF REPEATED GLUCOSE TOLERANCE TESTS IN THREE GROUPS OF PATIENTS: adults with hyperthyroidism, adults without hyperthyroidism, and children.

water, with a bit of citric acid added to the solution. Then samples of blood were withdrawn one-half hour, one hour, two, three and four hours after the ingestion of the glucose solution. The determinations of the blood sugar were made on one cc. of blood, with the Myers' modification of the Benedict method.

The object of this particular study was to note the effect of hyperthyroidism and of thyroidectomy on disturbed or normal carbohydrate metabolism, and to

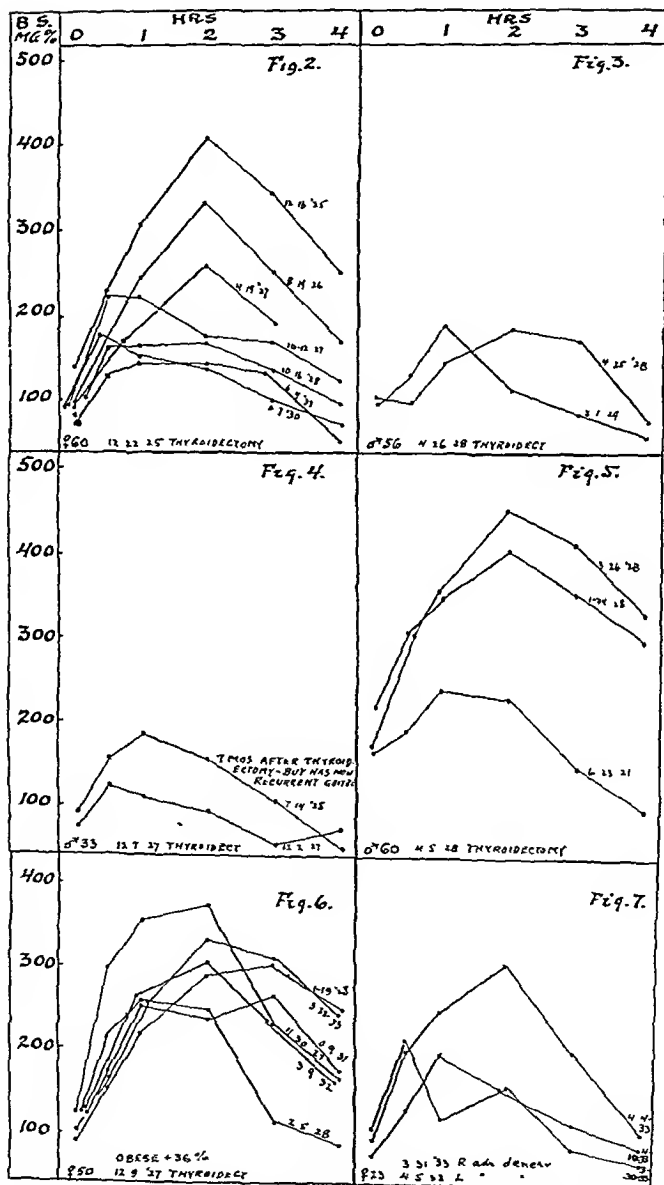


Fig. 2 GLUCOSE TOLERANCE TESTS IN CASE 1 Fig. 3 GLUCOSE TOLERANCE TESTS IN CASE 2 Fig. 4 GLUCOSE TOLERANCE TESTS IN CASE 3 Fig. 5 GLUCOSE TOLERANCE TESTS IN CASE 4 Fig. 6 GLUCOSE TOLERANCE TESTS IN CASE 5 Fig. 7 GLUCOSE TOLERANCE TESTS IN CASE 6

cent of patients with hyperthyroidism there was no change in the glucose tolerance curve, whether normal or abnormal, while the corresponding figure for the other groups of adults and children was 75.3 per cent and 72.2 per cent, respectively.

The following case records are typical of some of the individual variations in the behavior of the glucose tolerance curve in patients with hyperthyroidism.

*Case 1* shows the steady and progressive improvement in carbohydrate metabolism which may occur

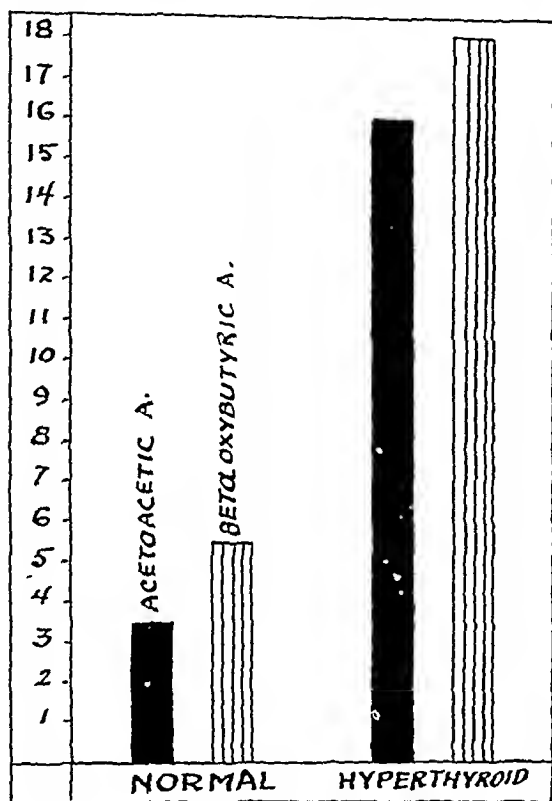


Fig. 8. THE CHANGES IN THE ACETO-ACETIC AND  $\beta$ -OXYBUTYRIC ACID CONTENT OF THE BLOOD IN HYPERTHYROIDISM.

following thyroidectomy even when the hyperthyroidism is severe. The patient was a woman, aged 60, whose B.M.R. was plus 41 per cent, when she was first examined on Dec. 16, 1925. She had lost considerable weight, and had glycosuria and hyperglycemia. The findings in successive glucose tolerance tests during the 12 years following show the steady improvement in the carbohydrate metabolism to a normal level (fig. 2).

*Case 2* shows that the response of the carbohydrate metabolism to thyroidectomy may not be immediate. The patient, a man, aged 56, who had previously been obese, had a B.M.R. of plus 50 per cent. He also had hypertension (190 mm. Hg systolic, 78 mm. Hg diastolic), and toxic peri-arthritis. He had glycosuria and slight hyperglycemia. Thyroidectomy was performed on April 26, 1928. On April 25, a glucose tolerance test showed a definite lag in the curve. Eight months later, however, the glucose tolerance curve was normal (fig. 3).

*Case 3.* In this instance the glucose tolerance curve, repeated 7 months after thyroidectomy, showed an impairment of carbohydrate metabolism which was accounted for by a recurrent goiter. The patient, a man, aged 33, had an adenoma of the thyroid, with hyperthyroidism. His B.M.R. was plus 15 per cent and he had mild hyperglycemia before operation which was performed on Dec. 7, 1927 (fig. 4).

*Case 4* shows the effect of hyperthyroidism on carbohydrate metabolism in a case of diabetes. The patient, a man, aged 60, had had diabetes for about 8 years when hyperthyroidism developed during the time he was using iodized salt. The B.M.R. was plus 50 per cent before thyroidectomy was performed, and at the same time, the level of the blood sugar reached its peak (fig. 5).

*Case 5* demonstrates the variations in the glucose tolerance curve over a period of more than five years in a case in which diabetes persisted after thyroidectomy. The patient was a woman, aged 50, who had an adenoma of the thyroid with hyperthyroidism. She was obese and displayed glycosuria and hyperglycemia when she was first examined. The basal metabolic rate at that time was plus 36 per cent. The blood pressure was 165 mm. Hg systolic, 90 mm. Hg diastolic. Since the thyroidectomy the patient has remained diabetic, although there has been some fluctuation in the glucose tolerance curve (fig. 6).

*Case 6* is interesting because it shows the effect on carbohydrate metabolism of adrenal denervation. The patient was a young woman with hyperthyroidism, aged 23, who at the time of the initial examination, displayed glycosuria, but the blood sugar was normal. The B.M.R. was plus 28 per cent and the blood pressure was 130 mm. Hg systolic, 70 mm. Hg diastolic. Denervation of the right adrenal was carried out on March 31, 1933, and five days later the glucose tolerance curve showed a sharp upswing (fig. 7). Five days after denervation of the left adrenal gland the level of the blood sugar following the ingestion of glucose was much lower.

#### DISCUSSION

The carbohydrate metabolism tends to be unstable in a considerable number of patients afflicted with hyperthyroidism. In a series of 9000 cases of hyperthyroidism, some disturbance was found in 7 per cent. There are a number of reasons for this finding in hyperthyroidism.

In the first place, patients with hyperthyroidism have an increased rate of metabolism which usually is accompanied by a marked increase in the intake of food consisting largely of carbohydrates. This places an additional load on the insulogenic apparatus, which, if there is a sufficient insulogenic reserve, withstands the added stress. If not, the carbohydrate metabolism is likely to break down under the strain.

The liver in hyperthyroidism is usually poor in glycogen. This has been proven by numerous experi-

mental investigations in which the feeding of desiccated thyroid gland to animals has been shown to result in a reduction of glycogen in the liver (3, 4, 5). Frazier (6) showed that the liver glycogen in control animals was 5.4 gm per cent, in animals that received thyroid extract, 0.82 gm per cent, in those that received thyroid plus potassium iodide, 0.12 gm per cent, and in those that received thyroid plus glucose, 0.17 gm per cent. Whether this is caused by the increased withdrawal of food reserves from the liver as the result of the higher rate of metabolism, or whether there is a disturbance in the mechanism of storage of glycogen in the liver, is still a question. The presence of mild acidosis may play a part in this phenomenon (fig 8). The fact that epinephrine, in the presence of a constant hyperglycemia, causes a marked depletion of glycogen from both the liver and the muscles (7) may also have a bearing. Hepatitis was demonstrated by Weller (8) in 50 per cent of a series of necropsies performed on patients with Graves' disease. Thus the presence of hepatitis may be a factor which affects the carbohydrate metabolism in hyperthyroidism.

In hyperthyroidism there is a marked increase in the ketone bodies in the blood (fig 8). In the presence of acidosis we know that the insulin requirement of diabetic patients under treatment increases, often strikingly. Whether this means that in the presence of a higher concentration of acids less insulin is secreted, or whether there is inactivation of the secreted insulin in circulation, has not been demonstrated clearly.<sup>1</sup>

There is also an accumulation of lactic acid in the blood stream in hyperthyroidism. This may be due either to an increased rate of production or to a decreased rate of removal. In normal animals the greater part of lactic acid which escapes oxidation to carbon dioxide and water is carried to the liver for synthesis into glycogen. Buell and Strauss (9) have shown experimentally that in hyperthyroidism the ability of the liver to convert lactic acid to glycogen is impaired. Figure 9 shows the results demonstrated by these authors, that is, the marked decrease of glycogen in the liver and the relative increase of lactic acid in the blood in hyperthyroidism.

From the foregoing facts, it would appear likely that both the pancreas and liver are involved in the

disturbance of carbohydrate metabolism which occurs in hyperthyroidism. The exact part played by each of these organs is difficult to estimate. If the liver alone were responsible for the impairment of carbohydrate metabolism observed in hyperthyroidism, we should expect a greater number of patients to return to normal after the hyperthyroidism has been eliminated by operation or treatment. There should be no cases of diabetes resulting from the disturbance in-

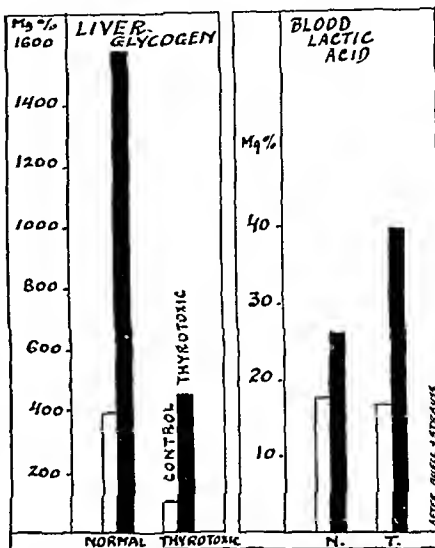


Fig 9 CHANGES IN THE GLYCOGEN CONTENT OF THE LIVER AND IN THE LACTIC ACID OF THE BLOOD IN THYROTOXICITY (After Buell and Strauss)

tiated by the hyperthyroidism, and certainly the incidence of diabetes should not be greater in hyperthyroidism than in the general population.

We know, however, that the incidence of diabetes is more than 100 per cent greater in patients with hyperthyroidism. The incidence of diabetes in patients with hyperthyroidism is 2.3 per cent (2), while in the general population it is about 1 per cent. This fact cannot be disregarded. Whether hyperthyroidism, with its increase in metabolism and its accompanying acidosis and hepatitis, also affects the insulogenic function of the islands of Langerhans is a point which needs to be elucidated by further experimental investigations. We know that hyperthyroidism not only causes temporary disturbances in carbohydrate metabolism, but also that it doubles the incidence of diabetes itself. Although we know some of the factors which contribute to this occurrence a

<sup>1</sup> Since the change is reversible up to this point which means by changing hyperglycemia to normal level. If this stage of hypoglycemia lasts beyond 3 months the reversible change is no longer possible and the changes in the islands go on to become permanent damage.

\* This shows the importance of controlling such an hyperglycemia in order to protect the islands from a possible permanent damage.

complete picture of the mechanism by which it is brought about is still lacking.

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# Studies of the Circulation and Respiration in a Patient with Anasarca Following Administration of Cortin and Sodium Chloride

## [Cortical Hormone and Circulation]

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EDEMA IS OF COMMON OCCURRENCE in patients with Addison's disease following treatment with desoxycorticosterone and sodium chloride (1-4). In addition to edema, some patients also exhibit dyspnea, reduced vital capacity, elevated venous pressure and roentgenographic changes suggestive of cardiac dilatation. It has been assumed that heart failure occurs under these circumstances, as a consequence of cardiac dilatation due to overloading the circulation with fluid. However, all of the patients thus far described had the decreased blood volume and abnormally small cardiac size found in Addison's disease. The present report is based on studies made in a patient without Addison's disease who developed massive generalized edema following administration of cortin and sodium chloride.

### REPORT OF CASE

B F (B I H #52040), a 43 year old man, with a past history of asthma, eczema and eosinophilia for many years and no evidence of adrenal cortical insufficiency, entered the hospital on Jan. 10, 1942, because of dyspnea and generalized edema. Twelve days before entry a dermatologist had prescribed daily doses of 50 gm of sodium chloride by mouth and 10 cc of cortin intramuscularly for the treatment of his eczema. At that time the blood pressure was 120 mm Hg systolic and 80 mm Hg diastolic, the serum protein level was 5.94 gm per cent and the erythrocyte count was 5,100,000 per cu mm. The patient received five daily injections of cortin. Five days before entry, marked swelling of the legs was observed. The dose of sodium chloride was reduced to 30 gm daily and cortin was given every other day for two doses. The edema rapidly involved the entire body, dyspnea and orthopnea developed, and the patient therefore entered the hospital. Examination revealed rapid respiration, orthopnea, dyspnea, edema of the face, distended veins in the neck, tachycardia, dullness and greatly diminished breath sounds over the lower portions of the lungs posteriorly, no rales,

enlargement of the liver 30 cm below the costal margin with slight tenderness on palpation, abdominal distension, edema of the arms, legs and trunk, and an eczematous lesion of the skin.

**Laboratory data.** The red blood cell count was 5,400,000 per cu mm, the hemoglobin was 90 per cent (Sahli), the white blood cell count was 12,100, and the differential was 74 per cent polymorphonuclear cells, 15 per cent lymphocytes, 3 per cent monocytes and 8 per cent eosinophils. The specific gravity of the urine was 1.024. Very large amounts of albumin and small numbers of red and white blood cells and granular casts were observed. The results of the stool examination were negative. Blood non protein nitrogen level was 37 mg per cent, serum protein level was 4.42 gm per cent, and the carbon dioxide combining power was 52 vol per cent.

Electrocardiographic tracings were normal.

Roentgenograms showed high diaphragm, moderate bilateral pleural effusion and congestive changes in the lungs. The heart was not enlarged.

**Clinical course.** The patient was given a salt poor diet with fluids limited to 1200 cc daily. Edema, hypertension and tachycardia diminished shortly after the patient entered the hospital, disappearing completely by the eleventh day of his stay (fig. 1). On the third day, ammonium chloride, 10 gm, was prescribed five times daily, but no detectable change resulted. During the first six days of the hospital stay, the rectal temperature rose to between 100.5° and 101.0° F every day, thereafter it was normal. Albuminuria rapidly diminished, but did not disappear until several days after all evidences of edema were gone (fig. 1). Granular casts, erythrocytes and leukocytes in the urine likewise were noted after the disappearance of all edema. The blood non protein nitrogen level was approximately 35 mg per cent on several occasions. The serum protein level rose to 5.98 gm on the ninth day of the patient's stay and to 6.54 on the eighteenth day (fig. 1).

### METHODS OF STUDY

The cardiac output was measured by the method of Starr and Gamble (5), all measurements being made with the patient in the semi-recumbent position in

the basal state. The oxygen consumption and respiratory minute volume were measured at the same time. The pulse and respiratory rates were counted 6 to 8 times during each determination. The arm to tongue circulation time was measured by means of decholin (6) and the lung to brain circulation time by means of carbon dioxide (7). The venous pressure was estimated by the direct method of Moritz and von

volume. It is clear, therefore, that the changes in respiratory dynamics in the patient of the present report were due to pleural effusion and not to congestive heart failure.

**Arterial oxygen saturation.** This was not strikingly low when first studied, although a significant increase did occur when the patient recovered. The changes are similar to those seen in other patients with pleural effusions (15).

**Venous pressure.** The venous pressure was moderately elevated during the height of the patient's illness, returning to normal after his recovery. This change is characteristic both of congestive failure (16) and of pleural effusion (15, 17), so that its occurrence in this instance is not diagnostic.

**Cardiac output and circulation time.** The cardiac output and arm to tongue and lung to brain circulation times were all within normal limits when the patient was dyspneic, orthopneic and severely edematous. This clearly rules out congestive failure as the cause of these signs and symptoms. There was a small increase in cardiac output following recovery. This resembles the slight increase in cardiac output observed by other authors following resorption of pneumothorax of small or moderate size (18).

**Clinical manifestations.** The patient's illness was characterized by the rapid onset of marked generalized edema, severe hypertension, dyspnea, orthopnea, profuse albuminuria and the occurrence of erythrocytes, leukocytes and casts in the urine. The serum protein concentration, normal before treatment with cortin and sodium chloride, fell rapidly to the low level of 4.42 gm. per cent. The manifestations, therefore, are similar to those of acute or subacute nephritis or toxemia of pregnancy. It is of interest in this con-

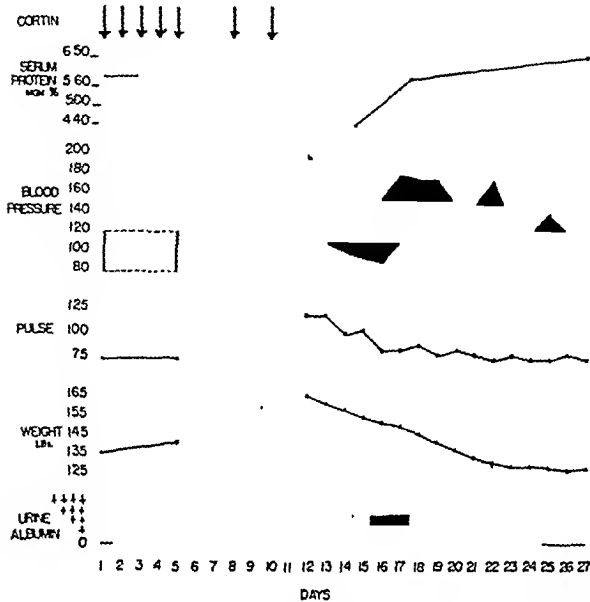


Fig. 1. RESPONSE OF PATIENT WITHOUT ADDISON'S DISEASE TO THERAPY WITH CORTIN.

Tabora (8). The lung volume and its subdivisions were measured by the method of Christie (9), modified somewhat (10). The arterial oxygen saturation was determined by means of the method of van Slyke and Neill (11), as modified by Fieser (12).

#### OBSERVATIONS AND DISCUSSION

**Respiratory dynamics.** The respiratory minute volume and rate were increased to twice normal while the patient was markedly edematous; the tidal air, however, was unchanged. The vital capacity was greatly diminished when first studied, the diminution being due to decreases in both reserve and complementary air volumes. The residual and functional residual air volumes were also decreased at this time. All of these volumes returned to normal after all evidences of edema had disappeared. The ratio of functional residual air to total pulmonary capacity was not abnormal at any time; it was 55.4 per cent when first studied, and 53.0 per cent after the patient had recovered. Congestive failure characteristically causes an increase in the ratio of functional residual to total capacity (13) and a decrease in tidal air. Pleural effusion, on the other hand, results in no change in the ratio of functional residual to total capacity (14, 15) and no striking change in tidal air

TABLE 1. MEASUREMENTS OF THE RESPIRATION AND CIRCULATION IN THE PRESENCE OF ANASARCA AND AFTER RECOVERY

|  | During             | After              |
|--|--------------------|--------------------|
| Decholin circulation time                      | 16.7 seconds       | 15.6 seconds       |
| CO <sub>2</sub> circulation time               | 6.8 seconds        |                    |
| Venous pressure                                | 14.0 cm.           | 5.1 cm.            |
| Cardiac output                                 | 3.76 liters        | 3.90 liters        |
| Cardiac output/100 cc. O <sub>2</sub> consumed | 1.57 liters        | 1.80 liters        |
| A-V difference                                 | 6.36 vol. per cent | 5.55 vol. per cent |
| Stroke volume                                  | 44 cc.             | 51 cc.             |
| Pulse  | 90                 | 77                 |
| Arterial O <sub>2</sub> saturation             | 93.1 per cent      | 98.2 per cent      |
| Oxygen consumption                             | 239 cc.            | 216 cc.            |
| Basal metabolic rate                           | +5.3 per cent      | -1.8 per cent      |
| Respiratory rate                               | 20                 | 10                 |
| Respiratory minute volume                      | 10.4 liters        | 5.06 liters        |
| Tidal air                                      | 520 cc.            | 506 cc.            |
| Residual air                                   | 1875 cc.           | 2420 cc.           |
| Functional residual air                        | 2370 cc.           | 3850 cc.           |
| Reserve air                                    | 495 cc.            | 1430 cc.           |
| Complemental air                               | 1905 cc.           | 3410 cc.           |
| Vital capacity                                 | 2400 cc.           | 4840 cc.           |
| Total capacity                                 | 4275 cc.           | 7260 cc.           |
| Functional residual air/total capacity X 100   | 55.4               | 53.0               |

nction that other authors (1, 3, 4) have noted the early appearance of edema of the face in patients receiving desoxycorticosterone and sodium chloride therapy for Addison's disease. Edema may occur following desoxycorticosterone medication even if the intake of sodium salts is maintained at normal levels (2). Albuminuria has also been described (1). Ferrebee et al (1) first suggested that congestive failure, resulting from cardiac dilatation due to overloading circulation with fluid, gave rise to the edema and dyspnea seen in such patients. However, their data (1) show that the extracellular tissue fluid volume increased very much more than the blood volume, indeed in one patient with severe edema and dyspnea, the blood volume was only 300 cc greater than it had been when the patient was free of these symptoms. Ferrebee et al (1) stressed increases in cardiac size following treatment with desoxycorticosterone, but McGavack (19) has shown that except for patients in crisis, changes in cardiac size in response to therapy in Addison's disease are not related to variations in blood volume. Conversely, a marked increase in blood volume does not cause cardiac dilatation and congestive failure. Neither patients with polycythemia vera (20), nor patients who have received large intravenous infusions at rapid rates of injection, exhibit cardiac dilatation or clinical or physiological manifestations of congestive failure (21, 22). Similarly, the hypertension which commonly develops after adrenal cortical hormone therapy (2) cannot be considered a consequence of an increase in blood volume (21). It must be concluded, therefore, that the clinical manifestations and physiological findings in patients exhibiting massive edema after therapy with adrenal cortical hormones and sodium chloride are not those of congestive failure secondary to overloading the circulation with fluid. The syndrome resembles closely that produced by the effects of a diffusely active vascular toxin, such as that which causes glomerulonephritis or toxemia of pregnancy. It is worthy of note in this connection that the administration of desoxycorticosterone to a patient with subacute glomerulonephritis aggravated the hypertension and resulted in an increase in the formed elements in the urinary sediment (23).

#### SUMMARY AND CONCLUSIONS

Studies were made of the clinical manifestations and cardiorespiratory physiology in a patient without Addison's disease who developed anasarca after the administration of cortin and sodium chloride.

The syndrome consisted in severe hypertension, generalized edema, effusions into body cavities, dyspnea, orthopnea, profuse albuminuria and lowering of the serum protein level.

The cardiovascular and pulmonary findings were those of pleural effusion; there was no evidence of congestive failure.

Cortin appears to act as a general vascular toxin in a manner similar to the substances which cause glomerulonephritis and toxemia of pregnancy.

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## Precautions for Pituitary and Thyroid Medication: Three Case Reports

**H**ypertension developing during thyroid and pituitary medication. A psychoneurotic maiden lady of 42 was examined January 2, 1936. She had sought treatment the preceding February for obesity, chronic fatigue and rheumatism. At that time her temperature was 99° F., pulse 82, blood pressure 145/95 mm. Hg, weight 211 pounds. The obesity was of the girdle type. Treatment had consisted of salicylates, foreign protein, sulphur and the usual remedies for rheumatism and arthritis. At the same time she had been put on a regime of reduced caloric intake and liberal doses of thyroid. Once or twice a week pituitary extracts had been injected, 0.5 cc. of an unstandardized extract of the anterior lobe and 0.5 cc. of the obstetrical variety of posterior lobe extract. During the eleven months she had lost 58 pounds in weight, but the symptoms were unchanged and the blood pressure had risen to 180/110 mm. Hg. Cessation of the thyroid and pituitary therapy had no effect on the blood pressure, and none of the measures usually employed for the control of essential hypertension has been effective. As a matter of fact, her blood pressure has risen and has since been as high as 210/110 mm. Hg.

She had had attacks of rheumatic fever at 15, 27 and 32 years of age and did not menstruate for 3 years following an appendectomy when she was 32 years old.

The patient had a marked urticarial outbreak a few hours after the first dose of posterior lobe extract, but when another manufacturer's product was used she tolerated it without unpleasant symptoms. The injections throughout the eleven months of treatment had not caused any discomfort. The hypertension was not accompanied by any of the symptoms often associated with or attributed to it.

Urticarial reactions to posterior lobe extracts are unusual and comparatively few cases are reported in the literature. In twenty years of active endocrine practice I have seen only four cases. Unfortunately we did not learn in any of these cases from what animal species the pituitary extracts had been prepared.

It cannot be said that the thyroid and pituitary injections caused the hypertension. As a matter of fact, we have had a few obese patients with hypertension whose blood pressure was reduced to normal levels by precisely the same treatment as this woman had. In some cases the blood pressure falls markedly after injections of extracts of either the anterior or posterior pituitary lobe. This case is cited only to call attention to the advisability of watching the blood pressure when a patient is on a prolonged regime of thyroid and pituitary medication.

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*Hyperglycemia after injections of pituitary extracts.* On April 25, 1941, a woman of 49 was seen who complained of obesity, limited largely to the lower half of the body, slight menopausal symptoms and constipation. She had gained 37 pounds since her marriage at the age of 34, when she weighed 96 pounds. She was 60¾ inches in height. Her B.M.R. was minus 7 per cent. The fasting blood sugar was 120 mg. per cent. After ingestion of 100 gm. of glucose, the blood sugar was 238, 187 and 164 mg. per cent at ½, 1½ and 2½ hours. No glycosuria occurred. The following day she was given 0.5 cc. of an unstandardized extract of the anterior lobe and the blood sugar rose in an hour from a fasting level of 125 to 230.7 mg. per cent. The day following she was given 0.3 cc. of obstetrical pituitrin and the blood sugar rose in one hour from a fasting level of 120 to 187.5 mg. per cent. No glucose was given with these tests. The rise in blood sugar presumably was due to the effects of the pituitary extracts. This type of response to pituitary extracts is not unusual and occurs often enough to warrant testing the patient's response to these substances before they are used as therapeutic measures. Pituitary extracts should not be administered to patients showing high blood sugar values during the glucose tolerance test nor to those exhibiting a marked rise in blood sugar after the injection of such extracts. While patients are taking thyroid and pituitary extracts, the blood pressure should be checked frequently and blood sugar determinations occasionally made.

In May the patient was given 10,000 i.u. of estrogen\* in 2000 unit doses at approximately four-day intervals. In June she received 2000 units on the 2nd, 5th, 9th and 12th. There was no treatment in July, August and September except with estrogenic hormone orally, 5000 units every third day. She had 2000 i.u. of estrogen on October 4th, 10th, 16th and 27th and on November 10th, 14th, 17th and 27th. On December 1st another glucose tolerance test was made. The fasting blood sugar was 112 mg. per cent. After 100 gm. of glucose the blood sugar was 164.2, 135.8 and 94.5 mg. per cent at ½, 1½ and 2½ hours, respectively, after the ingestion of the glucose. There was no glycosuria.

The administration of even small doses of posterior lobe extract within four days of the onset of a menstrual period will usually cause marked abdominal pain with the flow.

Thyroid given to obese young women frequently may upset the menstrual function and cause the periods to be delayed or even suppressed for a few months.

\* The estrogen (Amniotin) was supplied by E. R. Squibb and Son, New Brunswick, N. J.

Diabetes mellitus developing during treatment for hypogonadism. A boy, aged 14, was seen August 7, 1940, complaining that only one testicle was in the scrotum. The mother said he was sensitive, cried easily and lacked aggressiveness. In his early years he had had whooping cough, measles, scarlet fever and chicken pox. He was of normal height and about 10 pounds overweight. The genitalia were underdeveloped, but both testicles were in the scrotum. The BMR was minus 14 per cent. The blood count and urinalysis findings were normal.

He was given thyroid, one grain per day, APL gonadotropin 100 units twice a week and anterior pituitary extract 0.5 cc once a week. He received 8 injections in August and 3 in September. He was then given an extract of anterior pituitary in 0.5 cc doses 4 times in September, 8 times in October, 9 times in November and 8 times in December, 1940, 7 times in January, and 8 times in February, 1941.

In March he was given 6 injections of 100 u of APL gonadotropin. In April, because of a gain in weight, three minims of pituitrin was added to the APL. He received 8 injections in April, 6 in May and 4 in June.

Because the genital development was slow the APL gonadotropin was increased to 200 u and 5 minims of an

extract of posterior pituitary was given with it four times in June. He received three injections in July.

During a long automobile trip in the latter half of July he noticed marked thirst and between July 1 and August 5, 1941, he lost five pounds in weight. The urine had been examined frequently and the findings were normal. May 27, 1941. On August 5 there was marked glycosuria, some acetone and diacetic acid. The blood sugar was 333 mg per cent. On a diet of carbohydrate 140, protein, 90 and fat, 110 gm 30 u of insulin are required to keep the blood sugar within normal limits and the urine sugar-free. The patient has made a normal growth in height and the genitalia are now of normal size.

While the literature warns that glycosuria may develop in the course of such treatments, this is the first case I have seen. Dr. Chester Guy saw one such case. The glycosuria appeared shortly after treatment with pituitary hormones was started and disappeared under dietary restrictions. Such cases offer further support for the belief that the pituitary gland plays some part in the syndrome of diabetes mellitus.

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# CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. Collaborators: E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLIN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, EMMERICH VON HAAM.

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## GONADS

WIESBADER, H.

Oral therapy with pregnenolone in functional uterine bleeding. *Am. J. Obst. & Gynec.* 42: 1013, 1941.

Twenty patients were treated, the steroid being employed to stop bleeding; the highest daily dosage was 50 mg. It was found that 280 to 350 mg. were required to stop bleeding. Two patients yielded gestational responses. It is reported that 200 to 240 mg. of pregnenolone given during the latter half of the cycle will maintain cyclic and normal bleeding.—E.C.H.

WEISMAN, A. I., AND A. SCHWARZ.

Intersexuality proved by operation and microscopic examination. *J. Am. Med. Assoc.* 117: 2248, 1941.

A patient exhibiting unusual intersexuality had all the aspects of a female, but her gonads were definitely abnormally retained immature testes, and there was complete absence of ovarian tissue. Sufficient numbers of complete reports of such cases, when carefully studied may be capable of eventually explaining the etiology of such unnatural switches in nature.—C.P.

## HYPOPHYSIS

BOEHM, E. E.

Use of zipper in Friedman test. *Am. J. Clin. Path. Tech. Sec.* 5: 168, 1941.

The author recommended use of an ordinary 4 inch zipper placed in a midline incision in a rabbit for repeated examinations during the Friedman test. The first changes recognizable in the ovaries are small reddish-black spots which become noticeable as early as 10 hours after injection. The reaction reaches its height after 45 to 75 hours and the ovaries return to normal after 10 to 13 days. When the zipper is opened the first time numerous adhesions may be noted. After removing the zipper the incision heals rapidly.—E.v.H.

BREWER, J. I., H. O. JONES AND J. H. SKILES, JR.

Effect of gonadotropic substance on ovulation. *J. Am. Med. Assoc.* 118: 278, 1942.

A group of 24 female patients awaiting abdominal operation was treated with gonadotropic substance from 1935, and a group of 22 female patients was observed as controls. Only 2 of the treated patients showed signs of ovulation at operation. No multiple or new ovulations were induced. Ovulation occurred more uniformly in the control group.—C.P.

FRASER, R., AND PATRICIA H. SMITH.

Simmonds' disease or panhypopituitarism (anterior); its clinical diagnosis by the combined use of two objective tests. *Quart. J. Med. (New Series)* 10: 297, 1941.

The authors advocate the use of 2 tests as criteria in distinguishing Simmonds' disease from other similar pathologic states. The first was based on the patients' sensitivity of response to insulin, this being given intravenously, 0.1 unit per kilogram of body weight, after a 12-hour fast, a standard carbohydrate diet having been administered for the previous 4 days. Results were judged primarily by the speed of the fall in blood sugar and of recovery to the fasting level. In Simmonds' disease, the return to fasting blood sugar level is delayed and the 24-hour urinary excretion of 17-ketosteroids is below 0.5 mg. There are other disease conditions in which the response to insulin may be similar to that of Simmonds' disease or the 17-ketosteroid output may be extremely low. The authors present the results of these 2 tests in 10 cases which they diagnosed as having panhypopituitarism and in 15 other cases with allied syndromes including primary myxedema and anorexia nervosa.—J.E.H.

TWOMBLY, G. H., H. M. TEMPLE AND A. L. DEAN.

Clinical value of the Aschheim-Zondek test in the diagnosis of testicular tumors. *J. Am. Med. Assoc.* 118: 106, 1942.

A study of 203 cases of testicular tumor in which quantitative A-Z tests were done by the method of Ferguson and a study of 42 cases in greater detail, with a larger number of mice per assay level, revealed little correlation between the amount of gonadotropic hormone found in the urine and the histologic type of the tumor. Presence of chorionic gonadotropic hormone in the urine means an active tumor somewhere in the patient and suggests a bad prognosis.—C.P.

## PANCREAS

BEARDWOOD, J. T. JR., AND G. P. ROUSE, JR.

Diabetic acidosis. *J. Am. Med. Assoc.* 117: 1701, 1941.

The mortality rate for 200 cases of diabetic acidosis among 1,865 diabetic patients was 23.6% when cases with complications were included; when such cases were eliminated, it was 5%. Treatment used was M/6 Na lactate with adequate volumes of NaCl solution.—C.P.

GREENE, J. A., AND L. W. SWANSON

The utilization and effect of added dextrose *J Am Med Assoc* 118 364 1942

Carbohydrate was added to the usual regimen of patients with controlled diabetes in an unsuccessful attempt to differentiate between possible types of diabetes. Only 1 of the 56 patients failed to utilize the added sugar, whereas 18 required less insulin. Since such improvement indicated a beneficial effect, extra carbohydrate was added to the diets of 36 patients with uncontrolled diabetes. Only 1 failed to utilize the added sugar, whereas the urine of 15 promptly became free of sugar. There was no uniform response of blood sugar levels. It is postulated that depletion of the sugar stores of the body further reduces the ability of many diabetic patients to utilize dextrose and that the correction of this depletion improves the diabetes in such cases.—C P

## THYMUS

BLALOCK, A., A. M. HARVEY, F. R. FORO AND J. L. LILIENTHAL, JR.

The treatment of myasthenia gravis by removal of the thymus gland *J Am Med Assoc* 117 1529 1941

Confirmation of earlier operations where myasthenic patients were improved by thymectomy is provided by 6 additional cases. In 3 the improvement has been gradual, but definite. The authors conclude that thymectomy may be merely the breaking of a chain of abnormal events, although the data may indicate that the thymus is a gland with a functional internal secretion.—C P

## THYROID

BREITBARTH, B.

Study on the phosphate metabolism in congenital athyroidism *Ztschr f Kinderh* 62 52 1940

Lack of thyroid in the organism is followed by a decrease in inorganic P and an unfavorable Ca/P balance. On administration of thyroid in juvenile myxedema the low P content becomes normal or increased and on discontinuation of treatment this effect lasts for some time. Thyroid causes a retention of P and Ca, but does not influence N metabolism. In balance studies on rothyroidomized dogs the deficiency in thyroid was carefully compensated and evenly adjusted. On administration of thyroid the Ca and P balance is restored after a latent period and the excretion of both Ca and P in the urine is decreased. With subsidence of thyroid application, more Ca and P is excreted with the feces.—Erich Kaufmann (courtesy Chem Abstracts)

BROWN, R. B., E. P. PENDERGASS AND E. D. BURDICK.

The gastrointestinal tract in hyperthyroidism *Surg, Gynec & Obst* 73 766 1941

In human hyperthyroidism there is relative to the normal an increased incidence of achlorhydria, increased prominence of gastric rugae, a questionable increase in the time of onset of gastric emptying but a delay in the time required for complete evacuation of gastric contents and

an increase in both tone and motility of large and small intestine.—A T K

ENGEL, M. B., I. P. BRONSTEIN, A. G. BROOKE AND P. WESOLE

A roentgenographic cephalometric appraisal of untreated and treated hypothyroidism *Am J Dis Child* 61 1193 1941

In a study of 13 selected cases of hypothyroidism roentgenograms were made according to the technic of Broadbent. Bone development was judged by the Todd Standards. Craniofacial, dental and carpal ossification patterns of development of untreated children with hypothyroidism lag behind those of children given thyroid therapy. The deficiency lies in the occipital, parietal and, to much less extent, frontal area. The cranial base is shortened, and the spheno-occipital synchondrosis and the sutures of the vault are abnormally wide. The face shows a generalized retardation of growth as a result of the slowed velocity of growth of its components, that is, the mandible, the maxilla and the nasal bone. Teeth are delayed in eruption, without malformation. Differentiation and ossification of carpal centers are disturbed and retarded, and roentgenograms show persistence of infantile characters. Craniofacial dental and carpal patterns of development in untreated children with hypothyroidism are retarded. The differences from normal are merely an accentuation of those noted between treated and untreated cretins. Children with hypothyroidism treated regularly since early childhood closely approach normal levels of craniofacial and dental development. Thyroid deficiency affects craniofacial growth by retarding velocity rather than by modifying pattern.—M B G

ETICKSON, W. J., AND L. M. MORRISON

Role of liver and thyroid as metabolic factors in production of renal calculi *J Urol* 46 359 1941

Fifty nine patients with renal or ureteral calculi were studied. Of these 61% showed an abnormal BMR, 50% hypercholesterolemia and 59% liver dysfunction.—J C D

FOGGIE, W. E.

A lingual thyroid myxoedema following its removal *Edinburgh M J* 48 662 1941

A woman, 36 years old, had a cyst, which was causing mechanical interference, removed from the base of her tongue. The cyst wall was made up of thyroid tissue and no cervical thyroid could be detected. Myxedema developed and the patient was in coma when seen seven months after the operation. The symptoms were permanently relieved by thyroid feeding. The occurrence and significance of this rare condition are discussed.—J C D

HILDEBRAND, ALICE G., AND E. J. KEPLER

Familial periodic paralysis associated with exophthalmic goiter *J Nerv & Ment Dis* 94 713 1941

Familial periodic paralysis is a rare condition, 240 cases in all having been reported. It is marked by irregularly

occurring attacks of somatic muscular paralysis and inexcitability without sensory or psychic disturbances and good health in intervals between attacks. In the case reported, with the onset of exophthalmic goiter, the patient, who had previously suffered from occasional attacks of paralysis, began having frequent and severe attacks. The severity of the attacks was found to be closely correlated with the degree of depression of serum K. Attacks could be induced by injections of glucose-saline or by other agents which reduce blood K. Lugol's solution having been found inefficacious in relieving the disorder partial thyroidectomy was performed with entire relief. The hyperthyroidism was regarded as unmasking rather than causing the paralytic disorder.—R G H.

HIRSCHBERG, N., AND I. P. BRONSTEIN.

Note on a cretin's response to typhoid inoculation. *Am. J. M. Sc.* 202: 333. 1941.

In an investigation of the relationship of the thyroid to immunity a 22-year-old cretin was given typhoid vaccine. Subsequently repeated agglutination tests gave negative results. Following thyroid treatment at  $\frac{1}{2}$  to 2 grains daily strong agglutination reactions were obtained. No influence upon phagocytic activity could be detected.—R G H.

LERMAN, J.

The physiology of the thyroid gland. *J.A.M.A.* 117: 349. 1941.

In this review article the physiology is discussed under the following headings: histophysiology, thyroid hormone, potency of various fractions, blood I, relation to other endocrine glands, and the relation of thyroid to nutrition.—C P.

MASTER, A. M., AND JENNY STRICKER

Myxedema heart. Report of a case. *Ann Int Med.* 15: 123. 1941.

A case of hyperthyroidism is described in which the classical signs of myxedema heart appeared 10 years after operation for hyperthyroidism. After 6 weeks of thyroid medication the patient's general condition improved markedly, the B M R. became normal, dyspnea, fatigability and cardiac abnormalities disappeared. The heart, previously enlarged and of typical water-bottle appearance, became normal in size and configuration. Simultaneously the E K G, which had shown the characteristic low voltage of all deflections (QRS 4 mm.) became normal. Pericardial effusion is presented as a possible cause for the enlarged heart, the diminished cardiac pulsations and the low voltage E K G in myxedema heart.—*Author's abstract.*

RIGGS, D. S., E. F. GILDEA, E. B. MAN AND J. P. PETERS.

Blood iodine in patients with thyroid disease. *J. Clin. Investigation* 20: 345. 1941.

The blood I in 31 patients with hyperthyroidism ranged between 6.4 and 21.9 per cent; there was no overlapping with the normal range of 2.4 to 4.2 per cent. Seven patients with nodular goiters with no symptoms of over-

activity showed normal blood I. Elevated blood I values were invariably found in hyperthyroid patients, but high values were sometimes found in the absence of hyperactivity.—J. B. BROWN. (*courtesy Chem. Abstracts*)

SALTER, W. T., A. M. BASSETT AND T. S. SAPPINGTON.

Protein-bound iodine in blood. Its relation to thyroid function in 100 clinical cases. *Am. J. M. Sc.* 202: 527. 1941.

A series of 100 cases of suspected thyroid disturbance and 10 control individuals has been analyzed from the standpoint of final clinical diagnosis, B M R. and plasma protein-bound I. When the first two of these criteria are in agreement, there is a close correlation between the plasma I and the B M R. Such cases amount to 71% of the entire group studied. Of the remaining 29%, the B M R. often did not clearly reflect the clinical status and the plasma protein-bound I proved much more reliable. This was particularly true in the group of "Graves' disease without hyperthyroidism" in which the B M R. ranged from -20 to -40%, but the plasma protein-bound I was normal. These data therefore constitute additional evidence for the possible dissociation of physiologic hyperthyroidism and clinical Graves' disease. In hypothyroidism, plasma protein-bound I appears to be a highly reliable criterion for confirming lack of thyroid hormone, even when full-blown myxedema is absent. It has been emphasized that the simplified chemical procedures employed are partly empirical. Their use has been justified by their consistency with clinical data, but due care should be exercised in comparing the data with the results obtained by other methods.—*Authors' summary* (R G H).

SCHMIDT, C. R., W. S. WALCH AND V. E. CHESKY.

Liver insufficiency in toxic goiter and its treatment. *Surg., Gynec. & Obst.* 73: 502. 1941.

Liver function was tested by the hippuric acid test (oral) of Quick in 207 consecutive patients with goiter. Some impairment of liver function appeared in 55 per cent, 17 per cent showed reduction below 70 per cent of normal. The correlation between elevation of B M R. and depression of liver function was not perfect. Those with long standing hyperthyroidism with normal or slightly elevated B M R. were likely to have impaired liver function. While the role of heart failure in contributing to hepatic damage is recognized, this group is not specifically analyzed for this factor. Thyroid crisis and toxic psychosis were preceded or accompanied by severe liver insufficiency. Thyroidectomy was followed by a transient depression of liver function not due to sedative or local anesthetic. Liver function may be improved by a rather miscellaneous aggregate of procedures significantly called the 'works,' comprising added glucose with insulin, bile salts, liver concentrates and vitamin B.—A. T. K.

SCHWITTAY, A. M.

Occult hypothyroidism in Wisconsin women. *Wisconsin M. J.* 40: 475. 1941.

All patients with menstrual disorders should have

BMR determinations made, as a safeguard against missing those whom thyroid therapy would benefit. Use of the therapeutic test of thyroid medication rendered clinical results as good, in many cases, when the BMR was  $-8\%$  to  $-10\%$  as when it proved considerably lower. The menstrual disorders of patients with depressed BMR were alleviated by thyroid therapy — *HOH*

SHERILL, J W, AND E M MCKAY

Hypothyroidism and bladder function *J Urol* 46 34 1941

Twenty four rats, 170 days old, were divided into 3 equal groups. One group was thyroidectomized, one fed desiccated thyroid and the third kept as controls. The results are tabulated and illustrated with silhouettes of the bladder. The authors summarize "Atony of the bladder observed in patients suffering from hypothyroidism stimulated an experimental study of the relation of these conditions in the albino rat. Hypothyroid rats regularly showed bladder atony as measured by the filled area shown by a radio opaque compound in urine, bladder emptying time and the lowered ability to sustain an artificial increase in the intra bladder pressure" — *J C D*

SMOKVINA, M

Results of irradiation of the pituitary in Graves' disease and other forms of hyperthyroidism *Radiologia Clinica* 9 151 1940

The author describes the results of the recent experimental clinical and radiological investigations as to the action of the pituitary body in the production of Graves' disease and other conditions of hyperthyroidism. He reports the result of irradiation by X rays carried out between 1932 and 1936 on 50 such cases, at first only in women during the climacteric, but later also in younger women and in men. He describes fully the technic used at the Zagreb Institute. He considers that in such cases, when irradiation of the thyroid and thymus glands has not succeeded, the pituitary body should be treated, even when the condition of the patient has become worse, and certainly before an operation is performed — *Clinical abstracts*

SOFFER, L J, C COHN, E B GROSSMAN, MILDRED D JACOBS AND H SOBOTKA

Magnesium partition studies in Graves' disease and in clinical and experimental hypothyroidism *J Clin Investigation* 20 429 1941

In a series of 50 patients with Graves' disease a large proportion show a definite increase in nondiffusible Mg, the bound fraction varying between 25 and 61.6 per cent of the total serum Mg. There was no correlation between bound Mg and the BMR. In patients with Graves' disease of more than 2 years duration the nondiffusible Mg frequently tends to approximate normal levels. After treatment with I there is a marked drop in bound Mg, which is further lowered after subtotal thyroidectomy. In patients with myxedema, as well as with thyroidecto-

mized dogs, nondiffusible Mg is low or even absent. Thyroid returns to normal after administration of thyroid extract or thyroxine. The increase or decrease of bound Mg occurs at the expense of the ionizable fraction, since the total serum Mg remains unaltered — *J B Brown (courtesy Chem Abstracts)*

STARR, P, AND H POMERENZE

Therapeutic studies in hyperthyroidism *Ann Int Med* 15 226 1941

The effect of various medicaments administered, with chronological metabolism charts, is reported. An example of abrupt spontaneous remission after interruption of I tation is described. Desiccated thyroid, thyrotropic hormone, vitamin C, vitamin A, and testosterone were used in individual cases in very high doses, without benefit. Chorionic gonadotropin was given to 2 patients in whom remissions of hyperthyroidism occurred — *Paul Starr*

STEINER, M, AND A L NEWBOMB

Enlargement of the thyroid gland in juvenile patients with diabetes mellitus *Am J Dis Child* 61 458 1941

The occurrence of a palpable thyroid gland in juvenile diabetic subjects and its relation to the occurrence of diabetes and thyroid disease in the family have been investigated. Twenty per cent of the 128 subjects had a definitely palpable thyroid gland, and of these 50% had a history of diabetes and 80% a history of thyroid disease in the family, as compared with 19 and 12% respectively of the subjects with normal thyroids — *M B G*

SUTTON, R L

Acne vulgaris a pustular lipoidosis. Successful treatment based on control of lipid metabolism by low diet and thyroid extract *South M J* 34 1071 1941

The use of thyroid extract to tolerance in all cases described in connection with the dietary measures used — *J C D*

TALBOT, N B, G HOFFEL, H SHWACHMAN AND E TUOHY

Serum phosphatase as an aid in the diagnosis of cretinism and juvenile hypothyroidism *Am J Dis Child* 62 273 1941

Normal value for serum phosphatase for children 2 to 5 years of age is approximately 7 u with a range of from 5.14 u per 100 cc of serum. The level of phosphatase in plasma or serum is definitely higher in children than normal adults. The highest level is probably in the 4th to 5th month of life. The level tends to be depressed below normal limits in infants and children with untreated hypothyroidism (1.3 to 4.3 Bodansky u in cretinism and to 5.3 in juvenile hypothyroidism in this series). It is normal in mongolism. Since administration of adequate thyroid therapy raises the value, it is suggested that the level of serum phosphatase is a reliable index of thyroid deficiency in infancy and childhood — *M B G*

THOMPSON, W. O.

Thyroid dysfunctions and their treatment. *J.A.M.A.* 117: 441. 1941.

Thyroid dysfunction and pathology are discussed in this review article under the following headings: a) Primary and secondary hypofunction, b) Hyperfunction, c) Pathological states without altered function. The treatment, differential diagnosis, and complications of thyroid disorders are also discussed. There are also paragraphs on developmental anomalies, inflammatory conditions, and neoplasms of the thyroid.—C.P.

TOBIAS, M., AND L. STOCKFORD.

Measure of metabolic speed in children. *Am. J. Dis. Child.* 61: 675. 1941.

The assessment of delay in carpal development is not a measure of "slow metabolic speed." Determination of the level of total cholesterol is a simple and valid measure of a low level of maintenance B.M.R. activity in children. When the B.M.R. is within the so-called normal limits of  $\pm 10$  and  $-10\%$ , its normality must be verified by measures of both the total cholesterol and the skeletal development. Determinations of B.M.R. are less reliable than are determinations of total cholesterol as measures of "slow metabolic speed."—M.B.G.

WASS, S. H.

Diiodotyrosine in treatment of Graves's disease. *Lancet* 34. 1941.

In previously untreated cases the use of di-iodotyrosine as a preoperative measure was restricted to the most severe cases. In these it appeared to be entirely satisfactory, but showed no decided superiority over inorganic I. In patients who had had long courses of I before being referred to the surgeon, di-iodotyrosine produced remissions of sufficient degrees to allow of safe surgery. In this type of case the drug seems to produce better effects than can regularly be expected from iodine alone. In 2 cases a further remission was produced with a second course of di-iodotyrosine, but these figures are too small to allow of any definite conclusion. Thus, it seems to be possible to control the symptoms of hyperthyroidism by giving di-iodotyrosine periodically to patients awaiting operation, and still to get the patient into a good state for surgery when the time arrives. In hospital practice the drug may be very useful in this way, and further work may prove it of value in the routine medical treatment of Graves's disease.—*Courtesy Clin. Abstracts.*

WOKES, F.

The subcutaneous implantation of thyroxine tablets. *J. Pharmacol. & Exper. Therap.* 14: 165. 1941.

The effect of implanted thyroxine lasted about 3 weeks, and, since effects of this duration can readily be obtained by oral doses of thyroid, there is no obvious advantage in implanting tablets.—H. A. McGuigan (*courtesy Biol. Abstracts*).

YARDUMIAN, K. Y., AND N. M. WALL.

The relationship between blood cholesterol, sugar tolerance, and basal metabolic rate in thyroid disease. *Pennsylvania M. J.* 45: 239. 1941.

In cases of thyroid disease, with a rise in the B.M.R. there is a definite trend toward a lower serum cholesterol and decreased tolerance to glucose. And the reverse is true with a fall in the B.M.R. These trends are general, but in the more extreme cases the tendency towards a closer relationship becomes more pronounced. Exceptions are not uncommon.—I. B.

ZONDEK, H., M. MICHAEL AND A. KAATZ.

The capillaries in myxedema. *Am. J. M. Sc.* 202: 435. 1941.

In 8 women suffering from myxedema with typical mixedema hearts, the peripheral circulatory portion was subjected to exact investigation. In 7 cases the capillaries (ungual limbus) were markedly changed, the most striking feature being pronounced narrowness of the limbs. In some instances the loops only were recognizable. The number of visible capillaries was reduced. On thyroidin administration, the capillary picture as well as the clinical symptoms and the circulation time gradually returned to normal. No parallelism, however, could be established between the behavior of the capillaries on the one hand, and the general condition and the acceleration of the circulation time on the other hand. In the light of this evidence, the conclusion may be drawn that thyroidin is active in opening the arteriovenous anastomoses. Apparently the cross-section of the anastomoses as well as that of the capillaries is reduced in cases of myxedema, which is comprehensible in view of the abnormally reduced  $O_2$  requirements. In many cases myxedematous patients suffering from precordial pains similar to anginal states are likewise relieved by thyroidin administration. In this case, thyroidin is assumed to bring about a dehydration of the heart muscle (Zondek) and thus an increase in the blood supply of the heart. It is, therefore, suggested that development of precordial pains in myxedematous patients is not, as a rule, due to sclerotic changes of cardiac vessels, as generally assumed, but to mechanical impairment of coronary flow.—*Authors' summary.*



# The Journal of CLINICAL ENDOCRINOLOGY

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## Endocrine Studies on Human Hermaphrodites and Their Bearing on the Interpreta- tion of Homosexuality<sup>1</sup>

[Hermaphroditism]

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HUMAN HERMAPHRODITES fall into a number of discrete classes according to morphological appearance and probable causation (1). The origin of three is related to neoplastic growth of endocrine tissues, such as adrenal cortex (adrenogenital syndrome), ovarian medulla (arrhenoblastoma) and testicular blastema (chorioepithelioma of the testis). Their pathological nature, as well as the immediate causative factors, are easily recognizable. The afflicted individuals are distinctly *sick patients*, and operative removal of the tumors, if performed at the proper time, may restore normalcy, even with full reproductive capacity.

More enigmatical is the nature of sex intergrades of healthy appearance and without endocrine disturbances that might point directly toward the cause of their condition. However, it is fairly certain that many, possibly the large majority, of the cases have some hereditary background and that, with respect to the sex which suffers transformation, this heredi-

tary group is divided in two classes. In the first one, the daughters are normal while the *sons are hermaphrodites*. Transmission of the character is therefore possible only in the female line. The available records of affected families indicate that a dominant gene causes heterozygous mothers to produce hormones or hormone like substances which, in early pregnancy, effect a feminization of male fetuses. In accordance with expectations, half of the daughters prove to be carriers of this modifying gene. In typical cases, undescended testicles are present, together with ovarian tubes, uterus and vagina. At the time of puberty, male secondary sex characters begin to appear, with partial change of voice, male type of hair growth and enlargement of the clitoris. The complete range of variability of morphological features is not yet known (for complete discussion and references see reference 1).

It appears now that there exists a second class of hereditary hermaphroditism in which the female sex becomes afflicted. Within the last 4 years, two individuals clearly of this type presented themselves at the University Hospitals for remedial surgery. They had been reared as sisters. There are altogether

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mittee for Research in Problems of Sex.



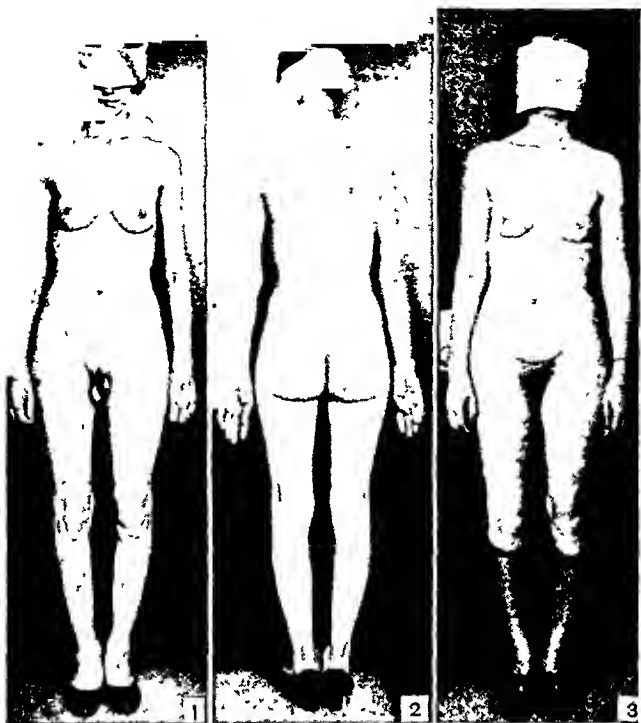


Fig. 1, 2. PATIENT 1. In preparation of the first operation, the pubic hair had been removed; the feminine straight top of the escutcheon is faintly visible. Fig. 3. PATIENT 1, 17 months after the second operation.

four siblings in this family: two normal boys and the two hermaphrodites. One boy is married and is the father of a son. In public appearance, both hermaphrodites give the impression of normal girls. Their parents also considered them to be predominantly

married, apparently without having a clear idea that their abnormality would interfere with marital life. The first patient came directly under our observation, the second only after having received treatment in another hospital. This report is therefore mainly based on the first patient, though it has been ascertained that the second is of nearly identical type.

#### *Description of Patient 1*

The older 'sister,' patient 1, came to the University Hospitals for the expressed purpose of the removal of two lumps which "got in her way when she danced with a man." 'She' assured the doctors that no other member of the family was similarly afflicted. Clinical examination revealed (fig. 1-3), in addition to the above data, dome-shaped breasts with well-developed nipples. The pubic hair presented a typical straight-topped feminine escutcheon. The chest was relatively small, and the hips wide, but not quite as broad as the shoulders. The legs and arms were relatively long and less feminine than the rest of the body. The patient had been engaged for some time in strenuous physical work and part of the muscular development may be attributed to exercise. Roentgenograms, made after the initial admission, revealed a bony pelvis of intermediate sexual type (fig. 4).

Curiously enough, this partly eunuchoid, partly feminine body was found associated with sex organs of predominantly male character (fig. 5). A bifid scrotum contained two well-descended testes (proved by bilateral biopsy), the right one larger than average



Fig. 4. PELVIS of patient 1. Fig. 5. EXTERNAL GENITAL ORGANS OF patient 1.

feminine, and reared them as girls. They had, when seen at the ages of 26 and 24, respectively, distinctly feminine voices. The skin was smooth, no beard was growing, and the breasts were well developed. Their interests also were of feminine orientation. Both were

size. The penis was small, about 5.5 cm. long, including the glans which measured 1.5 cm. It was completely formed except for the absence of the urethra, the meatus of which opened in a depression about two cm. below the base of the penis. Bilateral to this ori-

fice, there were small folds of tissue which continued anteriorly to form a frenulum for the penis. No vagina was evident and no prostate gland could be palpated on rectal examination.

Exploratory laparotomy proved the complete absence of female internal organs (uterus, tubes and ovaries). The cul de sac was entirely of male type, and structures closely resembling vasa deferentia were seen along each pelvic wall in a position normal for them. Biopsy specimens of the sex glands contained a few abnormal spermatozoa. The majority of seminal tubules were sterile.

Very interesting was the psychological attitude of this patient. 'She' had never been attracted by girls and, in spite of the failure of the first marriage, was in love with a man again. The medical adviser's proposal to make a surgical correction of hypospadias and to change the legal sex was very decidedly rejected. To the contrary, the patient insisted on having the external male organs removed and an artificial vagina made. She hoped that operation would bring about a change to enable her definitely to assume the feminine role, marry and produce children. Prior to knowledge that biopsy of the gonads revealed testicular tissue, she stated that she would be unhappy if informed that she were male rather than female.

The assay of urinary hormones gave a nearly typical female picture (table 1). Estrogens were present in considerable amount, tests with extracts from 300 cc of urine gave strongly positive reactions in castrated rats. Considering the imperfection of methods employed at the time, it is probable that the total estrogen content was not below that characteristic of urine of normal women. The androgenic hormones were so low that tests on the combs of chicks by local application gave no positive results, either before or after the operation, a liter of urine contained less than an equivalent of 0.1 mg of testosterone propionate. However, the presence of small amounts of male sex hormones was indicated by the considerable size and a good histological development of the epididymes. Apparently, enough androgens were released by the testes to stimulate these directly attached and probably most highly reactive organs, while the prostates, rudiments of which almost certainly must be present, remained too small for identification. We have no way of deciding whether the penis developed completely independent of hormonal stimulation. Tannate precipitates were negative for gonadotropins, at the level of one liter.

When, a month later, the individual returned to the hospital with unchanged attitude, it was decided to remove penis and gonads and attempt the construction of an artificial vagina with flaps secured from the scrotal skin. This was done, but the epithelial grafts did not take in the prepared cavity, which was al-

lowed to close after discharge from the hospital. As expected, the operation produced, endocrinologically, the castration effect. The estrogenic hormone disappeared from the urine, while the gonadotropic hormone rose within three weeks to more than 10 R U per liter. At an examination 3½ years later, 100 R U were found per liter (table 1). Before leaving the hospital, patient 1 began having fairly severe hot flashes with sweating. Two months after the operation, she had several of these flashes a day. Estrogen preparations were prescribed which gave complete relief. Before the operation, the breasts had been

TABLE 1. PATIENT 1, HORMONES PER LITER OF URINE

| Time                             | Gonadotropin, R U | Estrogen, R U | Androgen chick U |
|----------------------------------|-------------------|---------------|------------------|
| 1 month preoperatively           | Below 1           | Above 4       | Below 1          |
| Operative removal of both testes |                   |               |                  |
| 4 days postoperatively           |                   | Below 1       | Below 1          |
| 7 days postoperatively           | 2                 |               | Below 1          |
| 14 days postoperatively          | 6                 |               | Below 1          |
| 18 days postoperatively          | 6                 | Below 1       |                  |
| 21 days postoperatively          | 10                |               |                  |
| 3½ years postoperatively         | 100               |               |                  |

turgent, the individual even reported that they "swell" and "feel tingling" at monthly intervals. At the first examination, the left breast was slightly tender. After the operation, they became rather flabby (fig. 1, 3). The patient gained considerably in weight, which, however, may be due to concurrent change in living conditions. (The patient's weight changed from 121 lb at the time of the operation to 129½ lb two and one half months later.)

Direct questioning did not give a very clear picture of the change in sexual desire of this patient. As previously mentioned, both 'sisters' felt and behaved like normal women, they had their 'boy friends,' were married and wished to be married again. While patient 1 was in the hospital recovering from laparotomy and appendectomy, she was visited by a boy friend of whom the attendant doctor says "He seems to be a healthy, normal male of average intelligence." About this visit, the same doctor left the following report: "The two of them seem to be attracted to each other. They hold hands and whisper back and forth as any two normal lovers would." Six weeks after the second operation, the individual estimated that her sexual interests were reduced by one half.

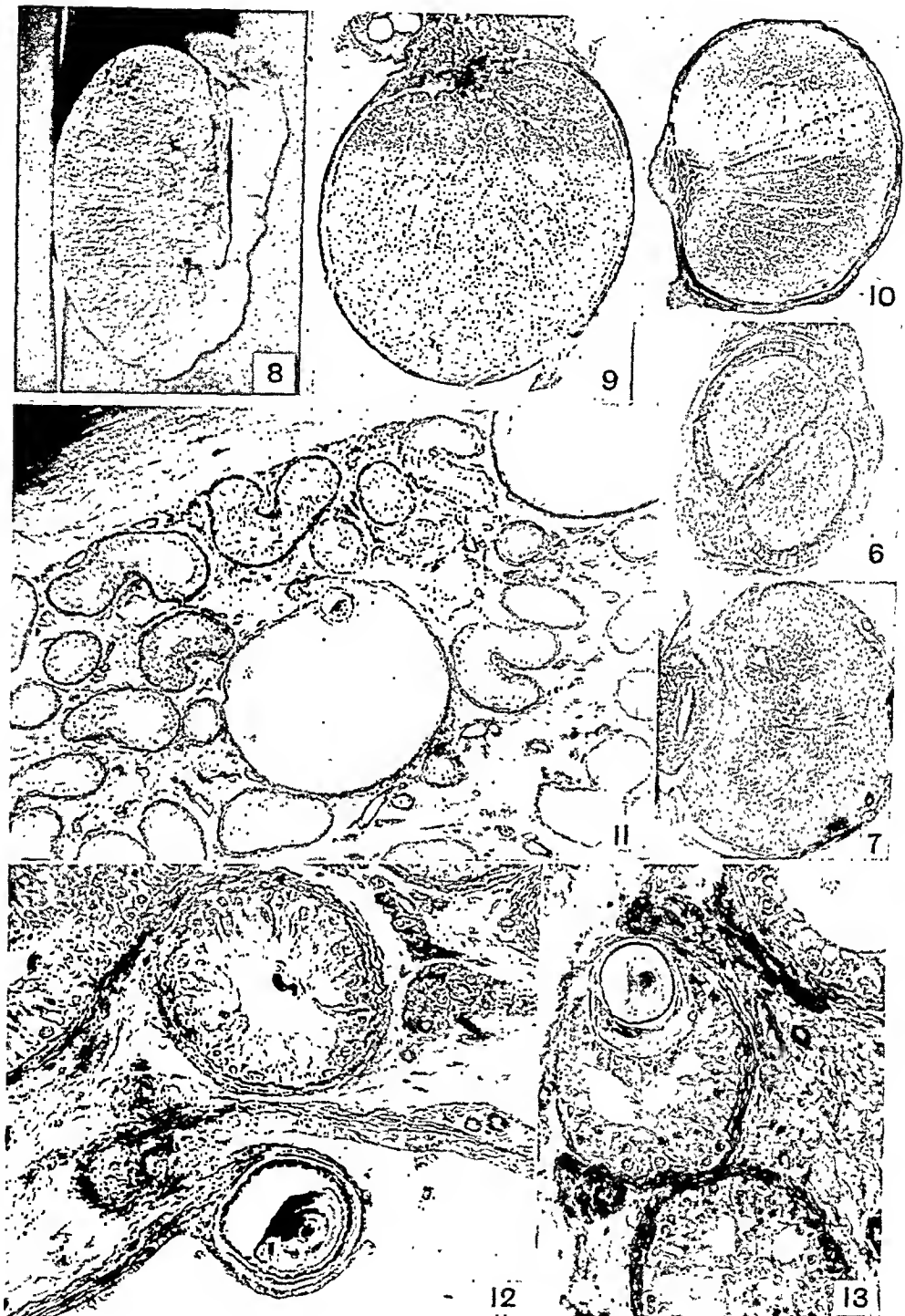


Fig. 6. CROSS-SECTION THROUGH PENIS OF *patient 1*.  $\times 2$ . Fig. 7. CROSS-SECTION THROUGH PENIS OF A NORMAL MAN.  $\times 2$ .

Fig. 8. HALF OF LONGITUDINALLY SPLIT RIGHT TESTIS, with attached epididymis of *patient 1*; natural size. Fig. 9. CROSS-SECTION THROUGH LEFT TESTIS OF *patient 1*.  $\times 2$ . Note 8 tubular cysts near the surface. Fig. 10. CROSS-SECTION THROUGH NORMAL TESTIS OF A YOUNG MAN.  $\times 2$

Fig. 11. PART OF A CROSS-SECTION THROUGH TESTIS OF *patient 1*. The seminal tubules are mostly sterile or near sterile. In the center is a large tubular cyst.  $\times 25$ .

Fig. 12. DETAIL FROM SAME SECTION as fig. 11 showing the glandular development of sustentacular cells in a seminal tubule and the egg-like body in a tubular cyst.  $\times 85$ . Fig. 13. EARLIER STAGE OF TUBULAR CYST with small central cavity. Cumulus-like arrangement of sustentacular cells around the egg-like body; a few spermatocytes and spermatogonia in the opposite wall.  $\times 85$ .

This statement is based on the fact that the presence of the boy friend no longer "bothers" her as it used to. This admission gains weight in view of the then intended—and later effected—second marriage. At the present time, this patient is happily married and refuses to submit to another operation for vaginal manufacture. Her husband, who is comfortably situated financially, is somewhat older than she. Coitus is performed, apparently to the husband's satisfaction, between the perineum and the upper and inner aspects of the closed thighs.

The tissues removed at the time of the operation were studied microscopically. At the present, only a summary account of the findings will be made. Cross sections through the penis (fig. 6) show the considerable size of the corpora cavernosa and absence of the urethra (comp. fig. 7).

The testes were excised together with the epididymes and some adhering tissues (fig. 8). In this condition, the left one weighed 29, the right one 49 gm. Since these testes were unmistakably the source of the estrogens produced during the preoperative period, a thorough search was made for eventual ovarian tissues. They were sliced in discs, and several thousand sections were cut, stained and studied microscopically, but no vestige of ovarian cortex was found. However, the glands are of a remarkable structure (fig. 9-13). Most of the seminal tubules have a smaller diameter than normal, which is due to the relatively low number of germ cells. Spermatogonia are present in most seminal tubules, and some of them are found undergoing mitotic division. Primary spermatocytes are rather rare and completely absent from many tubules. Some develop up to the metaphase of the first maturation division. Secondary spermatocytes or any further advanced spermatogenic stages are found but very exceptionally in these operative specimens, although it is an interesting fact that biopsy samples, taken one month earlier, had contained a few abnormal spermatozoa.

Since the testes were descended and suspended in scrotal sacs of normal dimensions, failure of completion of spermatogenesis must have been due to other causes than those working in cryptorchidism. The adversity of hereditary constitution and of hormonal conditions are the most likely factors responsible for spermatocyte degeneration.

As previously mentioned, a female basic constitution is indicated by the fact that the hermaphrodites have two normal brothers. Cytological study gives no indication of the presence of a pair of XY chromosomes. While admittedly, the analysis of human chromosomes offers considerable difficulties, it is significant that Feulgen stained primary spermatocytes contain no pycnotic elements that could be interpreted as sex chromosomes. The hermaphrodite

which recently was studied by Severinghaus (2) obviously belongs to the opposite sex-class.

The constitutional femaleness is probably the reason for the prevalence of estrogens noted in the hormonal output of the sex glands. The microscopical examination shows that the seminal tubules contain an abundance of sustentacular cells of Sertoli. Generally, they are of healthy appearance, and present the aspect of highly active secretory cells (fig. 12, 13). Distinctly, the most unusual feature of these testes is the presence of thousands of follicle-like vesicles in many seminal tubules, mainly within a zone near the distal surface of the testis (fig. 9, 11). Early stages show a slightly inflated tubular segment containing a cell, probably a germ cell with nucleus, that assumes in the cyst a position like that of the ovocyte in an ovarian follicle. This cell is encased in an envelope consisting of almost homogeneous albumen and resembling, except for its excessive thickness, the zona pellucida of the normal egg. The sustentacular cells appear in the rôle of the granulosa. In young vesicles (fig. 13), they are large, and form a hillock around the egg-like cell resembling the cumulus in the graafian follicle. In the largest vesicles, they flatten, slough off and degenerate while floating in the cyst-like lumen (fig. 11, 12). The wall of the seminal tubule, together with some attached interstitial cells, corresponds to the follicular theca, although giving a rather incomplete imitation. The parallelism of these features must be emphasized, because it offers the only histological clue as to the possible source of the female sex hormones. About the morphological homology of ovarian granulosa and testicular sustentacular cells, there remains little doubt, both arising from the follicle cells of the primordial gonia. The signs of high secretory activity indicate that sustentacular cells were the producers of the considerable amounts of estrogenic substances noted in this patient previous to the operation.

Clusters of interstitial cells of Leydig are present, though they are small and do not give the impression of much activity.

#### *Description of Patient 2*

Four years after patient 1 was seen, there appeared a young woman at the University Hospitals complaining of "failure to menstruate." Despite the difference in married names, she was soon recognized as belonging to the same family. Patient 2 was not as evasive and secretive as her 'sister,' although her confidence was not gained until gratitude for the successful manufacture of a functional vagina overcame her diffidence. It was from patient 2 that the family history was obtained. Both of these individuals recognized the bizarre nature of their deformities and, for this reason, were antagonistic to any suggestion

of direct inquiry among relatives. *Patient 2* consulted her home physician who removed the external genitalia and discarded the gonads. We did not, therefore, have an opportunity in this case for histological and hormonological studies. However, the physician, as well as the patient, assured us, after viewing photo-

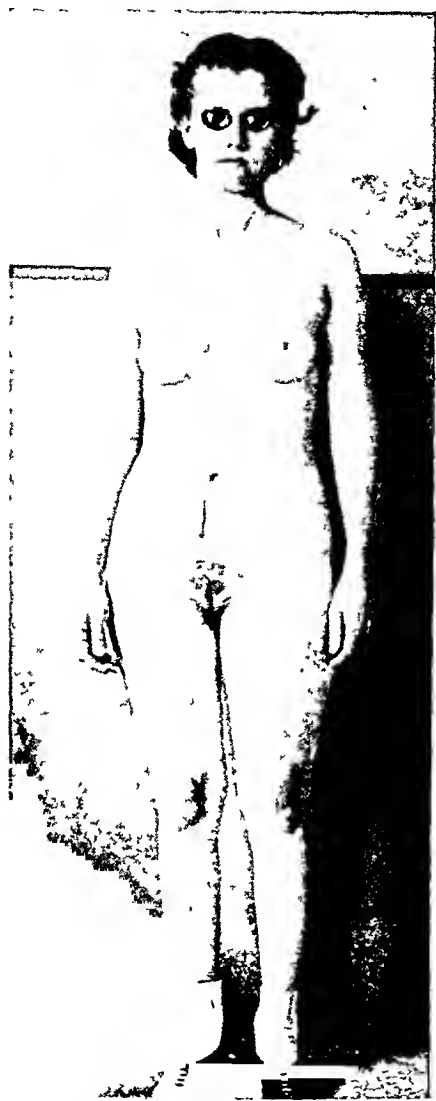


Fig. 14. PATIENT 2, one year after removal of external genital organs.

aphs of the genitalia of *patient 1*, that those of *tient 2* were similar in appearance.

On examination of *patient 2*, the external body conformation was that of a female (fig. 14). The extremities were not so muscular and therefore slightly more feminine in appearance than those of *patient 1*. There was no facial hair, the voice was feminine and the pubic hair presented the feminine type of escutcheon. The hips were almost as wide as the shoulders, and a roentgenogram revealed a quite typical female bony pelvis (fig. 15). The perineum was scarred, but two small folds resembling nymphae were present. The

urethral meatus was directly in front of the symphysis, having been drawn upward by scar tissue. The base of the incompletely removed penis provided clear evidence that this organ originally was of equal size as in *patient 1*. There was no evidence of a prostate gland on rectal examination. The family physician who, at the time of the first operation, had performed a laparotomy with appendectomy reports that no feminine internal genitalia were detectable. Complete absence of abdominal sex glands was definitely ascertained by our hormone tests which revealed the typical castrate condition. Urine samples collected one year after the operation contained 20 R.U. of gonadotropic hormone per liter.

Having tried one marriage, *patient 2* conceded that 'she' wanted to be married again, provided we could



Fig. 15. Pelvis of *patient 2*.

make her a vagina. This procedure was successfully accomplished by removing a one-piece, partial-thickness graft from the abdominal wall with the Padgett dermatome and supporting it with a suitable obturator in a cavity dissected between rectum and bladder.

Four months after this operation, the patient returned for observation, having been married for one month. The artificial vagina readily admitted two fingers for a distance of 9 cm. The 'mucosa' was thrown into folds closely resembling the rugae of a normal vagina, but there was little moisture present.

She claimed to enjoy coitus, experience definite sexual sensation, admitted that orgasm was lacking, but assented that she could hardly expect more. Most of the time artificial lubrication was necessary for intercourse. Overhearing a chance remark that the vagina was not as long as at the time of discharge from the hospital, she became a trifle indignant and stated that under sexual excitement, it lengthened and enlarged in diameter. Her husband is perfectly

satisfied with the vagina. She volunteered the information that she had gained weight and felt better physically than she had for years. Perhaps this sense of physical well being represents a reflection of an improved mental state, since she no longer has any sense of essential difference from other women.

#### DISCUSSION

The case of these hermaphrodite 'sisters' becomes of particular interest because there remains little doubt that basically they are of the female sex, in spite of nearly complete male sex organs. They differ from numerous cases of 'male pseudohermaphroditism' and hypospadias in the complete absence of male puberal sex characters. The general proportions of the body of the first patient were prevalently female, although distinctly shifted in the eunuchoid direction. Those of the second were nearer the female type. This raises the question of the factors determining skeletal growth. Roessle (3), reporting on a 37-year-old congenitally agonal woman, points out that the pelvis is not of the mature female, but of juvenile or neutral type. Therefore, the female skeletal traits observed in our patients can be considered as indications of hormonal, rather than of immediately genetical, conditions.

On the other hand, reports on individuals born without gonads agree in that the genital ducts are sexually differentiated. This suggests genetical (chromosomal) determination of prepuberal somatic sex characters in man and independence of their early embryological differentiation from gonadal factors. However, the cases of baby girls with adrenal hyper trophy prove that abnormal hormonal conditions may interfere and induce deviations from the normal course of self differentiation. There are no indications, in our two patients, of adrenal or other endocrine abnormalities. The problem of primary sex differentiation and the prenatal development of the genital ducts of the two cases remains therefore an unsolved problem. The assumption that the two hermaphrodites were basically of female sex merely expresses the conviction that they take the place of the expected female offspring in the family. Yet to all appearances, their hereditary constitution deviates from that of normal females. This genic variation may be the immediate and only cause for the peculiar hermaphrodite type of the early course of sexual differentiation, but the possibility of hormonal interference through the placenta must also be left open.

There appears still another side to this case, in fact a most provoking aspect, suggesting possibilities of far-reaching implications. Assuming the described two individuals, partially sex-reversed females, had been declared, legally, as of the male sex, then their inclinations and instincts obviously would mark them

as homosexuals. Now we have to take into consideration the fact that many 'pseudohermaphrodites' have been described which differ from our two patients only in various degrees of development of puberal male sex characters, change of voice and growth of hair. Therefore, the question arises as to what extent homosexuality may rest on sex reversal. That a large proportion of homosexuals is of a purely environmental type is clearly brought out by studies like the most recent one by Henry (4). However, indications of the existence of a congenital and probably hereditary type are numerous. Assuming that a certain number of homosexuals do arise by sex reversal, one must expect the occurrence of corresponding deviations from the normal sex ratio within their families. Intrauterine transformation of female fetuses should increase the male index and transformation of male fetuses should increase the female index. Of foremost interest in this connection is a statistical analysis, by Lang (5, 6), of the families of about 4,000 male homosexuals with police records. His material became available through the circumstance that in Germany, homosexuality among men has been made a criminal offense by laws adopted in 1871. From Lang's data, it appears that: a) Among brothers and sisters of homosexuals, the sex proportion is abnormally high and in favor of the male sex (2,078 brothers, 1,685 sisters, ratio 123:100). b) Among paternal half-brothers and half-sisters, the sex ratio is even higher (153 half-brothers, 113 half-sisters, ratio 135:100). c) Corresponding maternal half-brothers and sisters show an excess in the female sex (210 half-brothers, 234 half-sisters; ratio 90:100). d) Children of married homosexuals men show the normal sex distribution (143 sons, 136 daughters; ratio 105:100).

Barring the possibility of errors due to small numbers or inadvertent selection, both improbable in the case of this apparently very conscientious work, Lang's data lend themselves for interpretation as follows. Points a and b indicate that the fathers of some homosexual 'men' are carriers of a gene which, if transmitted to daughters, causes female-to-male sex reversal. Their sex-reversed offspring are potential homosexuals and contribute largely to this group. In an older study, Weil (7) reports that homosexual men as a group show body proportions which deviate from the normal partly in the female (large pelvic diameter) and partly in the eunuchoid direction (long arms and legs). In conjunction with our own observations, this may be interpreted as supporting the thesis of sex reversal as a source of homosexuality.

Point d may be taken as evidence that only 'environmental' homosexuals are fertile and capable of reproduction. They produce, as one would expect, an offspring of normal sex proportion. The low average number of children (1 per couple) indicates

widespread sterility. It may be due to total sterility of the hereditary (sex-reversed) group of homosexuals.

Point c requires no special discussion in this paper. It may indicate that some homosexuals are men partially feminized through maternal hormonal influences, as described in an earlier analysis (1) of cases reported by various authors.

On the basis of the data so far available, one still hesitates to make any definite statements concerning frequency of sex reversal in the human race. We had become accustomed to look at human sex determination as a solved problem, as a toss-up between X and Y chromosomes. Deviations of sex ratio, and of morphological and endocrine physiology, as well as of behavior, were only considered as oddities. Now as matters of sex are no longer shrouded with deep secrecy, we begin to realize that aberrations due to modifying genes and special hormonal conditions are much more prevalent than ever suspected. Many of them appear in set patterns and with a surprising regularity. While this may not be yet the time to express opinions about the relationship of sex reversal to certain sex abnormalities prominently affecting human society, it certainly seems timely to start systematic and comprehensive studies in this field in which, so far, little else than collections of case histories has been produced.

#### SUMMARY

1. Two remarkably similar cases of hermaphroditism are described with prevalence of maleness in the prepuberal and of femaleness in the puberal sex characters. The mental attitude was distinctly of female orientation.

2. Since the two are siblings and have two normal brothers, it is assumed that they are basically of female sex. Chromosome studies support this interpretation.

3. As most likely causes of the deviations, appear either a change in sex-determining genes or special hormonal conditions during pregnancy.

4. Evidence is presented supporting the contention that the sustentacular cells of the seminal tubules were the producers of the female sex hormones which predominated in the hermaphrodites prior to castration.

5. After operations involving castration and some plastic surgery, both individuals obviously were satisfied in their rôles as married women.

6. The possible importance of the cases for the interpretation of sex reversal and homosexuality in man are discussed.

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# Monomethyl Ether of Stilbestrol and Menopausal Syndrome

## [Stilbestrol Monomethyl Ether]

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MANY NATURAL AND SYNTHETIC compounds are estrogenic, but until recently only the natural compounds have been used clinically. Diethyl stilbestrol represents the first synthetic compound of acceptable clinical value. Since it is a well known fact that the derivatives of a compound may possess properties enhancing its clinical uses over that of the original, many derivatives of stilbestrol have been studied by Geschickter and Byrnes (1), and by Dodds, Lawson and Noble (2). It has been found that increasing the length of the side chain of stilbestrol decreases the potency, and esterification with aliphatic acids decreases potency but gives a more prolonged estrus. Sondern, Sealey and Kartsonis (3) and Geschickter and Byrnes (1) have studied the estrogenic effects of dimethyl, diethyl, and dipropyl ethers of stilbestrol giving the ratio of activity as 1:5:10:33. Geschickter and Byrnes (1) have found that the monomethyl ether was as potent as diethyl stilbestrol and more potent than estrone. In addition to their animal experimental work they evaluated the clinical effect of monomethyl ether in 19 cases of menopausal syndrome. The results compare favorably with those from diethylstilbestrol. They claim that side reactions, namely, nausea and vomiting, were not as marked.

Table 1 shows the data on 36 cases of menopausal syndrome treated with monomethyl ether of stilbestrol. A detailed history in the examination of each case is not given as this is not essential in the clinical evaluation of the results obtained. The cases are classified as natural, surgical and radiation menopause with sub classifications of mild, moderate and marked.

There were 25 cases of naturally occurring menopause, of which 3 derived no clinical benefit, 4 had fair, and 18 showed good to excellent results. Of these 17 had none of the side reactions noted above, 8 had slight to moderate reactions, and in only one case was it necessary to discontinue the chemical because of

side effects. One patient was willing to endure the reactions for the subsequent relief she received. After the third monthly dose of 25 mg intramuscularly she developed a tolerance to the chemical so far as side reactions were concerned, without any loss of relief of menopausal symptoms and is now taking one mg per day orally with practically no discomfort. One case had slight nausea with oral administration and none when the substance was given intramuscularly.

There were 7 cases of surgical menopause, 1 of which failed to respond to therapy, 1 responded poorly, 1 fairly, and the remaining 5 showed good results. Only 2 cases in this group had side reactions, and some patients claimed that the clinical effects were as good as with diethylstilbestrol, and better than some natural estrogens.

There were 4 cases of radiation menopause, in 1 of which the clinical effects were not as good as with diethylstilbestrol, while in the other 3 good results were obtained.

Considering the total number of 36 cases, 89 per cent derived clinical benefit and 11 per cent showed no response to treatment. Those not responding to monomethyl ether of stilbestrol did get relief with some one of the natural estrogens. Many of the 89 per cent had been treated previously with diethyl stilbestrol and claimed as good and in some instances better results. One patient, treated with every known estrogen claimed better results with monomethyl ether of stilbestrol. Of the 36 cases, 11 (30%) complained of side reactions, though some of these acquired a tolerance for the chemical.

The general method of treatment was to give 0.5 to 1 mg daily by mouth, or from 5 to 25 mg monthly by injection, depending upon the clinical response. In some patients 10 mg monthly in one injection sufficed, others required 25 mg. The doses necessary for the individual were arrived at empirically. Generally 1 mg per day orally or 25 mg a month intramuscularly seemed to suffice.



TABLE 1. RESULTS OF THERAPY WITH MONOMETHYL ETHER OF STILBESTROL

| Case;<br>Age,<br>yr.                              | Dose,           | Mg.,<br>Route | Interval      | Results   | Side Reactions               | Number<br>Months<br>Treated | Remarks   |
|---|-----------------|---------------|---------------|-----------|------------------------------|-----------------------------|---|
| Natural type of Menopause; a) mild symptoms       |                 |               |               |           |                              |                             |   |
| 1, 37   | 1               | Oral          | Daily         | Excellent | Nausea                       | 2                           | Symptoms disappeared after weeks  |
| 2, 54   | 1               | Oral          | Daily         | Excellent | None                         | 1                           |   |
| 3, 44   | 10-20           | Oral          | Monthly       | Good      | None                         | 2                           | Estradiol better<br>Menstrual migraine  |
| 4, 45   | 25              | Injection     | Monthly       | Poor      | Moderate                     | 10                          |   |
| 5, 31   | 1               | Oral          | Daily         | Good      | None                         | 3                           |   |
| b), Moderate symptoms                             |                 |               |               |           |                              |                             |   |
| 10, 51  | 20              | Injection     | Monthly       | Good      | Slight                       | 4                           | Poor case   |
| 11, 33  | 20              | Injection     | Monthly       | Fair      | None                         | 1                           |   |
| 12, 44  | 10              | Injection     | Monthly       | Fair      | None                         | 3                           |   |
| 13, 45  | 10              | Injection     | Monthly       | Fair      | Moderate                     | 3                           |   |
| 14, 48  | 10              | Injection     | Monthly       | Good      | None                         | 7                           |   |
|   | 1               | Oral          | Daily         | None      | Slight                       |                             |   |
| 15, 50  | 25              | Injection     | Monthly       | Good      | None                         | 7                           |   |
| 16, 41  | 10              | Injection     | Monthly       | Good      | None                         | 9                           |   |
| 17, 47  | 25              | Injection     | Every 6 weeks | Good      | None                         | 7                           |   |
| 18, 51  | 25              | Injection     | Monthly       | Good      | None                         | 8                           |   |
|   | 1 $\frac{1}{4}$ | Oral          | Daily         | Good      | None                         |                             |   |
| 19, 44  | 25              | Injection     | Monthly       | Good      | None                         | 3                           |   |
| 20, 54  | 15              | Injection     | Monthly       | Fair      | Moderate                     | 6                           |   |
|   | 1               | Oral          | Daily         | Fair      | Moderate                     |                             |   |
| 21, 46  | 25              | Injection     | Every 6 weeks | Good      | None                         | 8                           |   |
|   | 1               | Oral          | Daily         | Good      | None                         |                             |   |
| 22, 52  | 25              | Injection     | Monthly       | Good      | None                         | 4                           |   |
| c), Marked symptoms                               |                 |               |               |           |                              |                             |   |
| 30, 48  | 5-10            | Injection     | Bimonthly     | None      | None                         | 3                           | Could not tolerate diethyl<br>stilbestrol   |
| 31, 52  | $\frac{1}{2}$   | Oral          | Daily         | None      | Marked headache              | $\frac{3}{2}$               |   |
| 32, 46  | 1               | Oral          | Daily         | Good      | None                         | 4                           | Willing to tolerate for relief  |
|   | 50              | Injection     | Monthly       | Good      | None                         |                             |   |
| 33, 51  | 10              | Injection     | Monthly       | Good      | None                         | 12                          |   |
| 34, 47  | 25              | Injection     | Monthly       | Excellent | Nausea 1st 3 in-<br>jections | 8                           |   |
| 35, 46  | 25              | Injection     | Monthly       | Good      | None                         | 4                           | Better than estradiol benzo-<br>ate   |
| 36, 50  | 50              | Injection     | Monthly       | Good      | None                         | 5                           |   |
| Surgical Type of Menopause; a) moderate symptoms  |                 |               |               |           |                              |                             |   |
| 40, 53  | 10              | Injection     | Every 3 weeks | Good      | None                         | 5                           | Results comparable with<br>those with diethylstil-<br>bestrol                                 |
|   | 1               | Oral          | Daily         | Poor      | None                         |                             |   |
| 41, 46  | 25              | Injection     | Monthly       | Good      | None                         | 3                           |   |
| b) Marked symptoms                                |                 |               |               |           |                              |                             |   |
| 50, 33  | 25              | Injection     | Monthly       | Good      | None                         | 5                           | Treated with every avail-<br>able estrogen, mono-<br>methyl ether of stilbes-<br>trol better. |
| 51, 53  | 5-10            | Injection     | Weekly        | None      | Moderate                     | 1                           |   |
| 52, 51  | 20              | Injection     | Monthly       | Fair      | None                         | 1                           | No relief with 5 mg. orally<br>Endometritis   |
| 53, 28  | 25              | Injection     | Monthly       | Good      | None                         | 4                           |   |
|   | 1               | Oral          | Daily         | Good      | None                         |                             | Better than estrone   |
| 54, 38  | 20              | Injection     | Monthly       | Good      | Slight                       | 6                           |   |
| Radiation Type of Menopause; a) moderate symptoms |                 |               |               |           |                              |                             |   |
| 60, 50  | 1               | Oral          | Daily         | Good      | Slight nausea                | 2                           | Diethylstilbestrol better   |
| 61, 50  | 1-2             | Oral          | Daily         | Fair      | None                         | 1                           |   |

TABLE I. RESULTS OF THERAPY WITH MONOMETHYL ETHER OF STILBESTROL

| Clin. Age, yr      | Dose,   | Mg., Route        | Interval         | Results      | Side Reactions | Number Months Treated | Remarks                        |
|--------------------|---------|-------------------|------------------|--------------|----------------|-----------------------|--------------------------------|
| b) Marked symptoms |         |                   |                  |              |                |                       |                                |
| 70, 41<br>71, 46   | 1<br>25 | Oral<br>Injection | Daily<br>Monthly | Good<br>Good | None<br>None   | 4<br>5                | Better than diethylstilbestrol |

## SUMMARY

A series of 36 cases was treated with monomethyl ether of stilbestrol and 89 per cent of these responded favorably, while 11 per cent received no benefit from treatment. Many of those at first showing side reactions acquired a tolerance for the chemical without loss of clinical effects, and in only one case was it necessary to discontinue the treatment entirely. These results are encouraging and certainly compare favor-

ably with results obtained with other forms of estrogen therapy.

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# Clinical Use of Methylstilbestrol<sup>1,2</sup>

[Methylstilbestrol]

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SINCE THE ESTROGENIC PROPERTIES of diethylstilbestrol were first described by Dodds and associates (1) in 1938, extensive clinical work has been done to determine the estrogenic potencies and possible toxic effects of this drug (2-6). Its use by a number of investigators in various clinics has demonstrated pronounced estrogenic potency and mild toxicity, the latter consisting of nausea and occasional vomiting in a small percentage of cases. Various laboratory procedures used to determine possible specific organic damage from the drug have been negative in the hands of most investigators (2, 7).

Aside from the diethyl group attached to the stil-

therapy. The conclusions from the latter work were that the monomethyl ether of stilbestrol was a highly effective estrogen with less toxicity, as observed from clinical symptoms, than diethylstilbestrol. When it was used intramuscularly, in oily solution, these writers were under the impression that the estrogenic effect was more prolonged.

The present report concerns the clinical use of the monomethyl ether of stilbestrol, commonly known as methylstilbestrol, on 25 cases necessitating estrogen therapy. Eighteen cases were treated for menopause symptoms, 3 for amenorrhea and 4 for dysmenorrhea.

For the most part, the drug was administered by mouth in dosages varying from 2 mg. in 40 days to 390 mg. in 13 days. Occasional cases were treated by intramuscular injection. Toxic effects of methylstilbestrol occurred in 4 cases, consisted of nausea and vomiting only, but were not severe enough to necessitate cessation of therapy in any case. The occurrence of toxic manifestations was equally divided between oral and intramuscular administration

and their interpretation was entirely on a clinical basis. Since blood studies and liver and kidney function tests had been made previously on cases receiving diethylstilbestrol (2) it was not considered necessary to repeat them in this series.

Of the menopause cases, 5 were surgical, 4 followed radiotherapy and 9 were physiological.

These were members of a larger menopause group, all of whom had originally received small doses of phenobarbital; and the 18 treated with methylstilbestrol were the members of this group who had not been relieved by the former therapy. Nine of these patients received complete relief from this particular

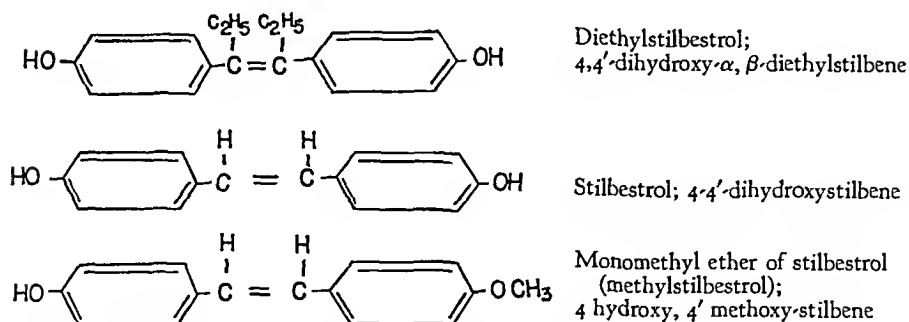


Fig. 1. Two STILBESTROL COMPOUNDS WHICH HAVE PROVEN ESTROGENIC POTENCY SHOWN WITH THE BASIC STILBESTROL FORMULA

bestrol base, a number of other substituent groups have been used to formulate other compounds which might have estrogenic potency.

Geschickter and Byrnes (8) assayed a large number of these different stilbestrol compounds on animals, finding varying estrogenic potency; and clinically assayed the monomethyl ether of stilbestrol on 9 cases of varying types necessitating estrogen

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<sup>2</sup> We are indebted to Dr. Franz C. Schmelkes of Wallace and Tiernan Products, Inc., Belleville, N. J., for a generous supply of methylstilbestrol.

TABLE 1 RESULTS OF TREATMENT OF PATIENTS WITH METHYLSTILBESTROL

| Case Number | Age years | Diagnosis    | Treatment  | Side Effects                                      | Results  |
|-------------|-----------|--------------|--|---|--|
| 1           | 52        | Menopause    | 2.5 mg daily for 14 days<br>2.5 mg every other day for 28 days                   | None  | Good   |
| 2           | 41        | Menopause    | 1.0 mg daily for 34 days   | None  | Fair   |
| 3           | 51        | Menopause    | 1 mg intramuscularly<br>1 mg daily for 52 days                                   | Moderately severe nausea,<br>slight vomiting      | Poor   |
| 4           | 53        | Menopause    | 5 mg intramuscularly, q 3-4 weeks  | None  | Good   |
| 5           | 39        | Menopause    | 1 mg intramuscularly per week  | Slight nausea and vomiting<br>after 3rd injection | Fair   |
| 6           | 43        | Menopause    | 0.5 mg 4 times a week for 4 weeks  | None  | Good   |
| 7           | 48        | Menopause    | 0.5 mg daily for 16 days<br>0.1 mg every other day for 26 days                   | None  | Good   |
| 8           | 49        | Menopause    | 1 mg daily for 7 days<br>0.5 mg daily for 21 days                                | None  | Good   |
| 9           | 50        | Menopause    | 2.5 mg daily for 21 days<br>2.5 mg daily for 21 days                             | None  | Good   |
| 10          | 49        | Menopause    | 1 mg daily for 14 days   | None  | Poor   |
| 11          | 50        | Menopause    | 1 mg intramuscularly for 9 days  | None  | Poor   |
| 12          | 34        | Menopause    | 0.5 mg daily for 28 days<br>0.5 mg daily for 42 days                             | None  | Fair   |
| 13          | 41        | Menopause    | 0.1 mg daily for 14 days<br>0.1 mg every other day for 21 days                   | None  | Good   |
| 14          | 52        | Menopause    | 1 mg daily for 30 days   | None  | Fair   |
| 15          | 48        | Menopause    | 0.5 mg daily for 28 days<br>0.5 mg every 3rd day for 60 days                     | Slight nausea and<br>abdominal pain               | Good   |
| 16          | 42        | Menopause    | 5 mg intramuscularly q 4 weeks<br>for 1 year                                     | None  | Good   |
| 17          | 38        | Menopause    | 1 mg daily for 13 days   | None  | Fair   |
| 18          | 46        | Menopause    | 0.1 mg every other day for 40 days   | None  | Fair   |
| 19          | 34        | Amenorrhea   | 0.5 mg daily for 85 days   | None  | Fair   |
| 20          | 24        | Amenorrhea   | 2.5 mg daily for 20 days, total,<br>50 mg  | None  | Withdrawal bleeding 2 days<br>after cessation of treatment |
| 21          | 20        | Amenorrhea   | 5 courses of 30 mg daily for 13 days,<br>total, 390 mg per course                | None  | Withdrawal bleeding follow-<br>ing each course             |
| 22          | 35        | Dysmenorrhea | 5 mg daily for 21 days<br>2.5 mg daily for 18 days                               | None  | Excellent  |
| 23          | 22        | Dysmenorrhea | 2.5 mg daily for 25 days<br>2.5 mg daily for 10 days<br>2.5 mg daily for 21 days | Slight nausea and<br>lassitude                    | Excellent  |
| 24          | 14        | Dysmenorrhea | 30 mg daily for 2 days<br>premenstrually   | None  | Excellent  |
| 25          | 29        | Dysmenorrhea | 2.5 mg daily for 21 days   | None  | Excellent  |

estrogen, 6 were improved and 3 unimproved (table 1). The amount of dosage could not be correlated with relief of symptoms.

It will be noticed from table 1 that case 3 developed nausea and vomiting following intramuscular injection but not following peroral therapy, and that

case 4 was relieved of symptoms for as long as 4 weeks by a single injection of 5 mg. intramuscularly and had no toxic manifestations.

Methylstilbestrol was administered to 3 cases of secondary amenorrhea.

One case ceased menstruating suddenly at the age of 34 and complete investigation of the patient's physical status (including basal metabolic rate, roentgenogram of the sella turcica and blood studies) revealed no abnormalities. Very thin atrophic endometrium was found at curettage. Over subsequent months massive estrogen and progesterone dosage, both separately and combined, produced no withdrawal bleeding, nor developed any endometrium. As a further trial, the patient was given small doses of this estrogen (0.5 mg. of methylstilbestrol) daily over a period of 3 months, during which time she had two periods of light bleeding lasting 3 days each, but there was still no evidence of endometrial proliferation on endometrial biopsy.

The second case of amenorrhea may well be considered a bad diagnostic error. A 24-year-old girl with a two-year history of amenorrhea was greatly disturbed concerning her failure to menstruate. The physical examination and laboratory workup, including basal metabolic rate, were negative. She was therefore given 2.5 mg. of methylstilbestrol daily over a period of 20 days and withdrawal bleeding occurred two days after cessation of treatment. At this time it was noticed that she had not had a pituitary roentgenogram, usually a routine procedure before starting therapy; and subsequent x-ray disclosed a large sellar tumor which was later diagnosed as a chromophobe adenoma of the pituitary. Further questioning of the patient revealed that she had been having 'eye trouble' for over 6 months consisting of frequent diplopia for which she was being treated elsewhere, and that she suffered from frequent headaches. She did not consider these symptoms of sufficient importance to mention them, which is, however, no excuse for our not having asked about them when her history was taken. Since these symptoms, plus the amenorrhea, were of comparatively long standing, it was not thought that the therapy was a contributory factor in the pituitary tumor formation.

This is a case in which an important diagnostic step had been neglected and it is presented in considerable detail to impress not only upon others, but upon ourselves, the importance of pituitary roentgenograms in all cases of amenorrhea.

The third case of amenorrhea complained also of pronounced hirsutism. Complete preliminary investigation proved negative and laparotomy disclosed no adrenal abnormalities but large ovaries filled with multiple small follicles, none of which, however, had grown to maturity. Several patients of this type with

similar pathological findings will be a subject for future report. In a later effort to check the hirsutism, however, this patient was given 30 mg. of methylstilbestrol daily in courses lasting 21 days and she had repeated periods of withdrawal bleeding.

The above three cases are presented here not so much because of their peculiar physiological abnormalities but more as evidence of the estrogenic effects of methylstilbestrol.

Of a large group of dysmenorrhea cases receiving estrogen therapy of various types, 4 were treated with comparatively large doses of methylstilbestrol.

In 3 cases (22, 23 and 25, table 1) the method of treatment was to give daily estrogen therapy throughout the first 21 days of the cycle in sufficient quantity to prevent ovulation, the resultant failure of progesterone secretion caused thereby producing a relief of dysmenorrhea (9). Complete relief of symptoms occurred in these 3 cases.

One patient suffering from dysmenorrhea was given 30 mg. of methylstilbestrol daily for 2 days just before the onset of menstruation and she also was completely relieved of symptoms.

These 4 cases indicate subjectively, at least, the estrogenic potency of methylstilbestrol.

One patient suffered from slight nausea at the beginning of treatment.

#### SUMMARY

The monomethyl ether of stilbestrol, commonly known as methylstilbestrol was administered in varying dosage to 25 cases necessitating estrogen therapy.

Eighteen menopause cases were treated. Nine were completely relieved, 6 were improved and 3 unimproved.

Withdrawal bleeding was produced in 3 cases of amenorrhea due to various abnormalities.

Four cases of dysmenorrhea were completely relieved of symptoms.

Transitory nausea and vomiting occurred in 4 of the 25 cases.

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# Estrogenic Content of Cirrhotic Livers

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IN 1934 ZONDEK (1) reported experiments indicating that the liver was capable of inactivating estrogens. This has been confirmed by other authors using a variety of methods. It would, therefore, seem logical to assume that the function of diseased livers might be impaired in this respect and that such livers might contain demonstrable estrogens.

While this piece of work was being completed, a paper appeared by Glass et al. (2). These authors, arguing along similar lines, studied the estrogenic content of urines from 14 cases with chronic liver disease. They found an increased amount of estrogens in every case. In 8 cases they assayed both the free and combined estrogens and found that the hormones occurred entirely in the free form, not in the combined form in which they are normally excreted. The authors concluded that their data indicated failure of cirrhotic livers to inactivate estrogens.

In the present study, the estrogenic content of liver tissue was determined.

## MATERIAL AND METHODS

Our material consists of livers obtained at autopsy from the pathological service here and from the Medical Examiner's service. In addition to the hormone studies, histological examinations were made of every liver.

The estrogens were extracted as follows. Fifty or 100 gram lots of liver were finely ground with a meat chopper, covered with 5 times their volume of acetone and allowed to stand for 24 hours at room temperature. The acetone was poured off and a fresh lot added to the tissue. After another 24 hours at room temperature, the second lot of acetone was filtered off and the tissue residue placed in the incubator for 2 to 3 hours in order to evaporate the acetone. The tissue was then covered with 5 times its volume of ether and allowed to stand at room temperature for 5 to 6 hours. The ether was then decanted and fresh ether added. The

first lot of ether was added to the residue obtained by evaporating the combined lots of acetone. After 18 to 20 hours the second lot of ether was filtered and this ether filtrate was added to the first lot of ether. The combined ethers were then filtered. Since many of the livers contained a large amount of fat, a method had to be adopted which would separate the estrogens from such fats. To do so we employed the method devised by Callow et al. (3). In brief this consists of shaking the ether extracts in a separatory funnel with 2N NaOH, acidifying the alkaline aqueous extract with concentrated HCl, extracting this with ether and finally evaporating the ether with the requisite amount of olive oil. We obtained a yield of approximately 50 per cent of the estrogens present by this method. The oil was tested for its estrogenic content on castrated female mice, primed each time 10 days before use by the injection of 8 i.u. of theelin.<sup>1</sup>

The total number of livers studied was 42. Of these, 23 were from cases of cirrhosis, 21 were of the alcoholic type, 1 was a pigment cirrhosis and 1 a biliary cirrhosis. The remainder consisted of a heterogeneous collection of conditions designed to serve as controls. Some were from normal individuals killed in accidents, others were from patients dying from a variety of diseases other than sepsis or tuberculosis, for we felt that such diseases might introduce a complicating factor.

The results together with certain pertinent data regarding each case are summarized in tables 1 and 2.

## COMMENT

It would seem worth while to comment briefly on certain of the data presented in tables 1 and 2 and on some additional data.

**Cirrhotic livers.** Of the 23 cases of cirrhosis, 15 contained demonstrable estrogens. An attempt was made to correlate the hormonal findings with the

<sup>1</sup> The theelin was supplied by Parke, Davis & Co., Detroit, Mich.

degree of cirrhosis, the presence or absence of bile stasis and the amounts of lipoid present but no such correlation could be established. Furthermore, the importance of the cirrhosis as a cause of death was considered but this did not appear to be relevant for liver damage due to cirrhosis leading up to the patient's death was as frequent in the positive as in the negative cases.

**Noncirrhotic livers.** Nine of the 19 noncirrhotic cases contained estrogens. The great majority of the livers in this group were histologically negative and

TABLE 1. CASES IN WHICH ESTROGENS WERE FOUND IN LIVERS

| Sex | Age       | Estro-<br>gens <sup>1</sup> | Liver<br>Pathology | Cause of Death          |
|-----|-----------|-----------------------------|--------------------|-------------------------|
| F   | yr.<br>61 | 55                          | Cirrhosis          | Carcinoma of pancreas   |
| M   | 59        | 100                         | Cirrhosis          | Cirrhosis               |
| M   | 70        | 80                          | Cirrhosis          | Cerebral hemorrhage     |
| M   | 84        | 40                          | Cirrhosis          | Cirrhosis               |
| M   | 70        | 80                          | Cirrhosis          | Erysipelas              |
| F   | 32        | 73                          | Cirrhosis          | Cirrhosis               |
| F   | 65        | 40                          | Cirrhosis          | Cirrhosis               |
| M   | 64        | 40                          | Cirrhosis          | Lobar pneumonia         |
| M   | 66        | 80                          | Cirrhosis          | Cirrhosis               |
| M   | 80        | 80                          | Cirrhosis          | Accident                |
| M   | 64        | 133                         | Cirrhosis          | Cirrhosis               |
| M   | 45        | 40                          | Cirrhosis          | Cirrhosis               |
| M   | 62        | 20                          | Cirrhosis          | Cirrhosis               |
| M   | 36        | 40                          | Cirrhosis          | Accident                |
| M   | 43        | 133                         | Cirrhosis          | Cirrhosis               |
| F   | 40        | 172                         | Negative           | Heart disease           |
| M   | 70        | 80                          | Central necrosis   | Bronchiogenic carcinoma |
| M   | 89        | 40                          | Negative           | Pernicious anemia       |
| M   | 70        | 40                          | Negative           | Gastric ulcer           |
| M   | 67        | 160                         | Negative           | Encephalomalacia        |
| F   | 59        | 20                          | Congestion         | Heart disease           |
| F   | 50        | 40                          | Negative           | Suicide                 |
| M   | 19        | 25                          | Negative           | Accident                |
| M   | 18        | 35                          | Negative           | Accident                |

<sup>1</sup> Expressed as castrated mouse units per kg. of wet tissue.

none showed any changes severe enough to interfere with function.

**Sex.** Nineteen of the positive cases were males and 5 were females. In the cirrhotic group, the livers of which contained estrogens, 13 were males and 2 were females. In the noncirrhotic group with positive hormonal findings, 6 were males and 3 were females. Five of the cirrhotic cases with negative estrogens were males and 3 were females. In the noncirrhotic group which contained no estrogens, 6 were males and 4 were females. In evaluating the significance of sex in this whole series there must be taken into account the fact that males predominated in a ratio of 2.5 to 1; furthermore that of the 23 cases of cirrhosis 18 were males.

**Age.** The age of the patients was not apparently a factor in explaining the presence or absence of hormones for the series covered a wide range. Two facts seem worthy of note. The first is that the livers of 2

normal males aged 18 and 19 respectively contained estrogens. The second is that the livers of some women past the menopause both cirrhotic and noncirrhotic contained estrogens.

**Testicular activity.** Tissue from the testicles of 14 of the cases was available for histological study. Ten of these were from the positive cases, 6 from the cirrhotic group. Five of these showed varying degrees of decreased activity while one was normal. Of the noncirrhotic group, 2 were hypoactive and 2 were normal. Of the testes from the cases with negative hormonal findings, 2 in the cirrhotic group were active, 1 was hypoactive. The testes from the one case in the noncirrhotic group with negative estrogens on which tissue was available for study were active. Therefore it would appear that the presence of estrogens in the liver is not dependent on loss or decrease of gonadal activity. Furthermore, it may be mentioned that in no instance was gynecomastia noted either clinically or at postmortem examination.

**Time postmortem.** It was felt that the time after death that the tissues were examined might have played a rôle in the hormonal findings since it is known that autolysis may have an influence on estro-

TABLE 2. CASES IN WHICH NO ESTROGENS WERE FOUND IN LIVER

| Sex | Age | Estro-<br>gens <sup>1</sup> | Liver<br>Pathology        | Cause of Death          |
|-----|-----|-----------------------------|---------------------------|-------------------------|
|     | yr. |                             |                           |                         |
| M   | 43  | -66                         | Cirrhosis                 | Cirrhosis               |
| M   | 76  | -59                         | Cirrhosis                 | Cirrhosis               |
| F   | 71  | -40                         | Cirrhosis                 | Hypertension            |
| M   | 59  | -40                         | Cirrhosis                 | Cirrhosis               |
| F   | 33  | -60                         | Cirrhosis                 | Alcoholism              |
| M   | 57  | -20                         | Cirrhosis                 | Heart disease           |
| F   | 50  | -55                         | Cirrhosis                 | Cirrhosis               |
| M   | 68  | -40                         | Cirrhosis and<br>hepatoma | Cirrhosis               |
| F   | 20  | -58                         | Negative                  | Glomerulonephritis      |
| F   | 38  | -20                         | Central necrosis          | Bronchiogenic carcinoma |
| M   | 24  | -40                         | Negative                  | Accident                |
| F   | 33  | -40                         | Negative                  | Alcoholism              |
| M   | 26  | -40                         | Central necrosis          | Heart disease           |
| F   | 48  | -40                         | Negative                  | Cerebral hemorrhage     |
| M   | 6   | -20                         | Negative                  | Accident                |
| M   | 10  | -20                         | Negative                  | Accident                |
| M   | 54  | -20                         | Negative                  | Accident                |
| M   | 70  | -20                         | Fatty infiltration        | Heart disease           |

<sup>1</sup> Figures indicate c.m.u. per kg. of wet tissue at which tests were negative.

gens. However, no correlation could be found between this factor and the estrogenic content of the livers.

In short, then, our original thesis that cirrhotic livers might contain estrogens was confirmed in part in that the majority of such livers contained estrogens. However, not every case did so. Furthermore, estrogens could be demonstrated in essentially normal livers from both males and females. The explana-

tion of this finding is not clear at the present time. Since we did not employ hydrolysis in extracting the hormones, it would seem probable that they existed in the free rather than in the combined form, our results in this respect agreeing with those of Glass et al (2).

#### SUMMARY

1 The livers from 23 cases of cirrhosis were examined for estrogens. Fifteen gave a positive result.

2 Nineteen noncirrhotic livers were similarly studied. Nine contained estrogens.

3 The presence of estrogens could not be accounted for by the degree of cirrhosis, the age, sex or gonadal activity of the patients.

4 The livers of some women past the menopause and of normal young men were found to contain estrogens.

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# Excessive Uterine Bleeding: Antigonad Effect of Pro- lactin

## [[Pituitary-Ovarian Relationship]]

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IN JUNE, 1937, the writer began clinical investigation of the effects of prolactin when administered during phases of excessive uterine bleeding. Thirty-five cases were reported in 1938 (1). During the clinical investigation of the effects of the lactogenic hormone on phases of excessive uterine bleeding, several preparations of prolactin have been used.<sup>1</sup> Information has been received from Lyons (2) that none of these has been pure lactogenic hormone. The prolactin used in the current series however, is sufficiently pure and potent to be used effectively for controlling excessive uterine bleeding, and the following report seems to justify its wider usage for this purpose. In every case in which there was no pathological condition such as fibromyomata, intra-uterine papillomata, or persistent thick-walled cysts, the lactogenic hormone therapy was satisfactory. Cessation of excessive bleeding in cases of fibromyomata has been obtained in variable percentages in each series of patients. The majority of patients are improved and several have continued to maintain normal menstrual functions without any surgical procedures for as long as 4 years. Endometrial hyperplasia, when not associated with a persistent cyst or tumor growth, may regress with prolactin and equine gonadotropin therapy.

Goldzieher observed that 'Uterine bleeding which is greater than normal in quantity or which occurs at too short intervals is looked upon as a sign of abnormal ovarian function' (3). Uterine bleeding in the presence of local pathological processes such as polyps, submucous fibroids or malignant tumors of the uterus is not functional in character and consequently cannot be expected to be cured by hormone therapy. There is, however, a hormonal pathogenesis of fibromyomata (4). Many patients who have fibromatous growths, have responded well to prolactin therapy,

and maintained normal menstrual function for many months after therapy has been discontinued.

In the presence of persistent follicle cysts it is difficult to control the disturbed physiology and the bleeding with the usual doses of prolactin. Three patients with palpable normal sized ovaries, and with no uterine growths present, continued to bleed excessively in spite of prolactin therapy. Subsequently, at laparotomy at least one follicle cyst was found in each patient.

Careful, complete physical examinations, B.M.R. determinations and endometrial biopsy records are made of each patient, and vaginal smears made during the non-bleeding phases.

One to two hundred international units of prolactin have been given subcutaneously during each day of the bleeding, usually in doses of 100 I.U. Beginning on the second or third day of the following period of menstruation, the hormone may be administered again daily, if the bleeding has been too heavy, and until the bleeding stops. If there is no excessive bleeding during the next menstruation, then equine gonadotropin therapy may be indicated, 2000 I.U. being given on the 9th, 10th, and 11th days of the cycle.

In this second series of reports, prolactin was administered to 56 patients of whom 34 had functional excessive bleeding, and 22 had fibromyomata at the first examination; several of these had various other conditions such as persistent follicle cysts which were diagnosed as surgical cases, because therapy relieved but did not cure the disturbance.

Of the 34 cases of functional excessive bleeding 33 improved with from 300 to 2400 I.U. of the prolactin in 3 to 24 doses for each patient, averaging 800 units per patient. One patient required 6300 I.U. over a total period of 24 months. This patient was 27 years old and had menstruated almost daily for 13 years. Treatment with 3600 I.U. of prolactin during 3 months, followed by 24,000 I.U. of gonadotropin during 4 months, resulted in apparently normal menstrual periods, for 11 months. Bleeding became prolonged again, although not excessive in quantity,

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TABLE 1 FUNCTIONAL BLEEDING CASES, NO GONADOTROPIN THERAPY

| Name     | Age | Duration of Bleeding                                  | B M R | Endometrial Biopsy           | Vaginal Smear Before Prolactin <sup>1</sup> | Duration of Prolactin Treatment | Total Dosage of Prolactin | Vaginal Smear After Prolactin | Biopsy After Prolactin, Remarks                           |
|----------|-----|---|-------|------------------------------|---|---------------------------------|---------------------------|-------------------------------|---|
| Mrs R W  | 46  | 21 days, 1st time                                     | +8    | Late estrogenic, 23rd day    | 4+ 23rd day                                 | 20 weeks                        | 1 U 1900                  | 2+ 24th day                   | 4 months after therapy menses ok, scanty                  |
| Mrs J G  | 41  | 10 days, 1 year                                       | -7    |                              | 3+ 10th day                                 | 5 weeks                         | 500                       | 4+ 25th day                   | Uterus smaller after prolactin                            |
| Mrs A B  | 49  | Irregularly throughout each month, 3½ years           | +5    | Atrophic, 20th day           | 2+ 20th day                                 | 15 days                         | 800                       | 1+ 28th day                   | No surgery  |
| Mrs A S  | 26  | 21 days, 1st time                                     |       |                              | 3+ 21st day                                 | 7 days                          | 400                       | 4+ 11th day                   | Urticaria after 4th day No further trouble Normal periods |
| Mrs A J  | 44  | 7 days, 2X monthly, 3 months                          | -4    | Early estrogenic, 18th day   | 2+ 18th day                                 | 2 days                          | 200                       | 2+ 18th day                   | Atrophic 18th day   |
| Mrs R W  | 46  | 21 days, 1st time                                     | +11   | Mild hyperplasia, 22nd day   | 5+ 21st day                                 | 6 weeks                         | 1000                      | 3+ 26th day                   | Early estrogenic 26th day                                 |
| Mrs E E  | 44  | 2-5 weeks, 4 months                                   | -3    | Late estrogenic, 36th day    | 5+ 36th day                                 | 6 days                          | 600                       | 3+ 42nd day                   | Late estrogenic 42nd day                                  |
| Mrs B G  | 49  | 23 days, 1st time                                     |       | Early estrogenic 23rd day    | 4+ 23rd day                                 | 4 days                          | 300                       | 2+ 27th day                   | Early estrogenic, 26th day                                |
| Mrs L H  | 41  | 6 days, (48 pads), 1st time                           |       |                              | 5+ 6th day                                  | 4 days                          | 400                       | 2+ 14th day                   | Menses normal there after                                 |
| Miss R B | 46  | 21 days, 1 year                                       | +5    | Cystic hyperplasia, 20th day | 5+ 20th day                                 | 9 weeks                         | 700                       | 4+ 10th day                   | Only slight improvement, pulmonary carcinoma              |
| Mrs A C  | 46  | Each mid month, days                                  | +3    | Early estrogenic, 10th day   | 4+ 10th day                                 | 14 weeks                        | 1400                      | 2+ 23rd day                   | Operation for intrauterine fibromyoma 8 years before      |
| Miss E C | 47  | 5 weeks continuous, then 2-3 weeks monthly, 10 months | +8    | Early estrogenic 18th day    | 3+ 14th day                                 | 6 weeks                         | 800                       | 2+ 14th day                   | Occasional scanty bleeding the following year             |

<sup>1</sup> Classification of vaginal smears (a) As of duration

and further treatment for 6 months with 3700 i u of prolactin was required to correct it. The patient received a total of 6300 i u of prolactin, at the end of which time she had a 6+ degree of vaginal cornification (5). This case gives evidence of the transitory effects of prolactin and the freedom from danger of abnormal physiological changes.

During a period of 4½ years more than 700 doses of prolactin, of 100 i u each, obtained from the various manufacturers, have been administered to a total of 160 patients. Nine had serum reactions within 20 to 90 minutes, these were manifested as mild generalized urticaria. All were comfortable within a few hours following adrenalin chloride therapy. None

TABLE 2. FUNCTIONAL BLEEDING CASES, GONADOTROPINS USED

| Name      | Age | Duration of Bleeding                                 | B.M.R. | Endometrial Biopsy                 | Vaginal Smear Before Prolactin | Duration of Prolactin Treatment | Total Dosage of Prolactin | Vaginal Smear After Prolactin | Gonadotropin, <sup>1</sup> Total Dose | Vaginal Smear After Gonadotropin | Biopsy and Comments   |
|-----------|-----|--|--------|------------------------------------|--------------------------------|---------------------------------|---------------------------|-------------------------------|---------------------------------------|----------------------------------|---|
| Mrs. M.H. | 24  | Scanty; continuous 6 months                          | -7     | Early estrogenic phase, 24th day   | 3+<br>24th day                 | 12 weeks                        | 1 U.<br>1000              | 3+<br>24th day                | 1 U.<br>24,000<br>4 months            | 6+<br>24th day                   | Normal periods  |
| Mrs. R.F. | 32  | 6 days<br>2 X month,<br>2 months                     | +4     | Mild hyperplasia, 14th day         | 4+<br>14th day                 | 11 weeks                        | 1000                      | 3+<br>14th day                | 24,000<br>4 months                    | 6+<br>18th day                   | Pregnant following month  |
| Mrs. L.Z. | 31  | 8 days,<br>2 X month,<br>7-8 months                  | +7     | Late estrogenic phase, 24th day    | 5+<br>24th day                 | 10 days                         | 300                       | 5+<br>24th day                | 18,000<br>3 months                    | 6+<br>18th day                   | Cystic ovary no longer palpable; follicle cyst removed 5 yr. before |
| Mrs. D.P. | 34  | 14 days,<br>1st time                                 |        | Late estrogenic, 14th day          | 5+<br>14th day                 | 2 weeks                         | 600                       | 3+<br>18th day                | 12,000<br>2 months                    | 6+<br>24th day                   | Menses 3 days a month since treatment                               |
| Mrs. R.J. | 27  | 8 days, very heavy,<br>2 months                      | -2     | Late estrogenic, 19th day          | 5+<br>10th day                 | 1 week                          | 600                       | 3+<br>17th day                | 24,000<br>4 months                    | 5+<br>18th day                   | Right ovarian follicle cyst. Pelvic adhesions                       |
| Mrs. M.H. | 24  | Spotting continuous 9 weeks;<br>2-5 week cycles      |        | No biopsy                          | 2+<br>8th day                  | 8 weeks                         | 900                       | 2+<br>10th day                | 18,000<br>3 months                    | 5+<br>19th day                   | Pregnant 5 months later   |
| Mrs. B.A. | 20  | 3 days,<br>2 X month,<br>9 months                    |        | Cystic hyperplasia, 8th day        | 5+<br>8th day                  | 2 weeks                         | 400                       | 3+<br>9th day                 | 18,000<br>3 months                    | 6+<br>18th day                   |   |
| Mrs. C.B. | 32  | 18 days,<br>1st time                                 | -6     | Late estrogenic, 14th day          |                                | 8 days                          | 500                       | 3+<br>24th day                | 24,000<br>4 months                    | 5+<br>18th day                   | Pregnant 2 months later   |
| Mrs. J.G. | 41  | 8-15 days,<br>1 year                                 |        | Early estrogenic, 12th day         | 3+<br>12th day                 | 4 weeks                         | 500                       | 4+<br>18th day                | 6000<br>1 month                       | 3+<br>18th day                   | Normal periods  |
| Mrs. L.C. | 23  | 2-3 weeks,<br>5 months                               | +2     | Late estrogenic, 10th day          | 4+<br>10th day                 | 23 weeks                        | 1400                      | 4+<br>24th day                | 18,000<br>3 months                    | 4+<br>18th day                   | Normal menstruation   |
| Miss J.B. | 18  | 10 days,<br>1 year                                   | +6     | Early estrogenic, 14th day         | 5+<br>14th day                 | 14 weeks                        | 500                       | 4+<br>21st day                | 24,000<br>4 months                    | 6+<br>18th day                   | Masculine hirsutes and body; virgin                                 |
| Mrs. G.G. | 49  | 10 days,<br>3 months                                 |        | Early estrogenic, 10th day         | 2+<br>10th day                 | 16 weeks                        | 900                       | 2+<br>14th day                | 6000<br>1 month                       | 4+<br>18th day                   | Normal flow thereafter  |
| Miss M.A. | 26  | 2 weeks,<br>3 years                                  | -4     | Mild cystic hyperplasia, 20th day  | 5+<br>20th day                 | 13 weeks                        | 1100                      | 3+<br>13th day                | 6000<br>1 month                       | 4+<br>18th day                   | One ovary out 6 years ago; curettment 3 years ago                   |
| Miss M.N. | 27  | 10 days,<br>9 months                                 | +4     | Mild hyperplasia, 10th day         | 4+<br>10th day                 | 1 week                          | 600                       | 3+<br>20th day                | 8000<br>1 month                       | 5+<br>18th day                   | Normal menses since   |
| Mrs. H.S. | 37  | 5-7 days,<br>2 X month,<br>5 months                  | -7     | Marked hyperplasia, 7th day        | 5+<br>7th day                  | 7 weeks                         | 400                       | 2+<br>21st day                | 18,000<br>3 months                    | 5+<br>18th day                   | Normal menses since   |
| Mrs. D.S. | 26  | 10 days,<br>4 months                                 | -7     | Late estrogenic, 18th day          | 5+<br>18th day                 | 9 weeks                         | 1000                      | 4+<br>20th day                | 18,000<br>3 months                    | 5+<br>18th day                   | Normal menses since   |
| Miss L.N. | 23  | 3 weeks,<br>4 months                                 | +3     | Late estrogenic, 18th day          | 4+<br>23rd day                 | 20 weeks                        | 600                       | 3+<br>26th day                | 10,000<br>2 months                    | 5+<br>18th day                   | Normal menses since   |
| Mrs. N.W. | 35  | 10 days,<br>5 months                                 | -6     | Early estrogenic, 8th day          | 5+<br>8th day                  | 16 weeks                        | 700                       | 3+<br>9th day                 | 18,000<br>3 months                    | 5+<br>18th day                   | Normal menses since   |
| Mrs. S.M. | 27  | 4 days,<br>2 X month,<br>2 months                    | +5     | Early estrogenic, 8th day          | 3+<br>8th day                  | 5 months                        | 1200                      | 3+<br>23rd day                | 24,000<br>4 months                    | 6+<br>20th day                   | Normal menses since   |
| Miss C.G. | 27  | 13 years,<br>almost daily                            | +8     | Mild hyperplasia, day of cycle (?) | 5+<br>Day of cycle (?)         | Total of 24 months              | 6300                      | 2+<br>9th day                 | 24,000<br>4 months                    | 6+<br>18th day                   | Early estrogenic, 9th day   |
| Mrs. C.O. | 21  | 10 days,<br>1st time                                 | +10    | Late estrogenic, 21st day          | 5+<br>21st day                 | 10 days                         | 100                       | 3+<br>21st day                | 12,000<br>2 months                    | 6+<br>18th day                   | Pregnant 2 months later   |
| Mrs. W.P. | 34  | Periods scanty followed by bleeding 27 days 1st time | +4     | Late estrogenic, 14th day          | 5+<br>14th day                 | 2 weeks                         | 600                       | 3+<br>14th day                | 12,000<br>2 months                    | 6+<br>16th day                   | Early estrogenic, 14th day  |

<sup>1</sup> Equine gonadotropin: 2000 I.U. per dose; three doses per month, administered on 9th, 10th, and 11th days of each cycle, for not longer than 4 months (12).

TABLE 3 CASES OF UTERINE FIBROIDS

| Name    | Age      | Duration of Bleeding               | B M R | Endometrial Biopsy           | Vaginal Smear Before Prolactin | Duration of Prolactin Treatment | Total Dosage of Prolactin | Vaginal Smear After Prolactin | Biopsy and Comments                                       |
|---------|----------|------------------------------------|-------|------------------------------|--------------------------------|---------------------------------|---------------------------|-------------------------------|---|
| Mrs GH  | 43       | 8 days, no bleeding previous 5 mo  | -5    | Late estrogenic, 8th day     | 4+<br>8th day                  | 1 week                          | 10<br>400                 | 2+<br>18th day                | Early estrogenic, 18th day no surgery                     |
| Mrs RH  | 24       | 18-10 days, 1 1/2 years            |       | Early estrogenic, 12th day   | 3+<br>12th day                 | 8 days                          | 800                       | 4+<br>21st day                | Late estrogenic 21st day no surgery                       |
| Mrs WL  | 30       | 11 days, 3 months                  | +5    | Cystic hyperplasia, 12th day | 5+<br>12th day                 | 12 weeks                        | 1100                      | 3+<br>18th day                | Cystic hyperplasia, 12th day, hysterectomy                |
| Mrs DW  | 33       | 5 days, 20 day cycles, 3 months    | +1    | Late estrogenic, 10th day    | 5+<br>10th day                 | 4 days                          | 300                       | 3+<br>26th day                | No surgery  |
| Mrs RM  | 47       | 10-20 days, scanty 18 months       | -7    | Early estrogenic, 24th day   | 4+<br>24th day                 | 7 days                          | 700                       | 3+<br>6th day                 | Early estrogenic, 24th day, no surgery                    |
| Mrs AF  | 41       | 21 days, 1st time                  | +3    | Late estrogenic, 22nd day    | 5+<br>22nd day                 | 3 weeks                         | 600                       | 3+<br>21st day                | No surgery  |
| Mrs LZ  | 46       | 8-12 days, usually early, 5 months | +4    |                              | 4+<br>26th day                 | 12 weeks                        | 700                       | 3+<br>26th day                | No surgery  |
| Mrs HZ  | 43       | 10 days, 3 months                  | -5    | Cystic hyperplasia, 12th day | 4+<br>12th day                 | 5 days, 7 mo later 7 days       | 300<br>700                | 3+<br>19th day                | Partial hysterectomy                                      |
| Mrs AE  | 48       | Excessive, frequent, 2 years       | +6    | Early estrogenic, 19th day   | 3+<br>19th day                 | 14 weeks                        | 1300                      | 2+<br>22nd day                | Uterus not easily palpable, no operation                  |
| Mrs RM  | 47       | 14 days, 6-8 week cycles           |       |                              | 3+<br>14th day                 | 1 week                          | 700                       | 3+<br>18th day                | 7 months after treatment menses normal, uterus smaller    |
| Mrs WW  | 49<br>49 | 2 weeks<br>2 months                |       | Late estrogenic, 10th day    | 4+<br>10th day                 | 5 days                          | 500                       | 2+                            | No surgery  |
| Mrs CH  | 44       | 10 days, 7 months                  | +3    | Early estrogenic, 10th day   | 5+<br>10th day                 | 13 weeks                        | 1100                      | 3+<br>17th day                | No surgery  |
| Miss EP | 35       | 2 weeks, 11 years                  | -9    | Late estrogenic, 18th day    |                                | 3 weeks                         | 800                       | 4+<br>18th day                | No surgery  |
| Mrs MB  | 49       | 2 weeks, 2 months                  | -5    | Cystic hyperplasia, 16th day | 5+                             | 4 weeks                         | 800                       | 3+<br>18th day                | No surgery  |
| Mrs RS  | 47       | 2 weeks, 2 months                  | +8    | Late estrogenic, 21st day    | 5+<br>21st day                 | 3 weeks                         | 1000                      | 3+<br>20th day                | No surgery  |
| Mrs SA  | 33       | 3 weeks, monthly, 1 year           | +6    | Mild hyperplasia, 24th day   | 5+<br>24th day                 | 1 week                          | 300                       | 4+<br>21st day                | No surgery  |
| Mrs OG  | 58       | 1st in 18 months, 5 weeks          | -7    | Atrophic, 35th day           | 3+<br>35th day                 | 2 weeks                         | 500                       | 2+<br>21st day                | Atrophic 21st day, myomectomy                             |
| Miss HH | 37       | 15-20 days, 5 months               | +1    | Early estrogenic, 22nd day   | 3+<br>22nd day                 | 4 weeks                         | 600                       | 2+<br>21st day                | Atrophic, 21st day no surgery                             |
| Mrs PB  | 32       | 10 days, 1 year                    | +14   | Late estrogenic, 10th day    | 4+<br>10th day                 | 3 days                          | 300                       | 3+<br>14th day                | Intrauterine fibroid size of walnut, partial hysterectomy |

TABLE 3—Continued

| Name      | Age | Duration of Bleeding              | B.M.R. | Endometrial Biopsy           | Vaginal Smear Before Prolactin | Duration of Prolactin Treatment | Total Dosage of Prolactin | Vaginal Smear After Prolactin | Biopsy and Comments  |
|-----------|-----|-----------------------------------|--------|------------------------------|--------------------------------|---------------------------------|---------------------------|-------------------------------|--|
| Mrs. D.Z. | 47  | 8-12 days, 21-day cycle, 5 months |        | Proliferative, 18th day      | 3+ 18th day                    | 10 weeks                        | I.U. 700                  | 3+ 24th day                   | 1 year after therapy, fibroids seemed smaller; menses scanty; no flushes                   |
| Mrs. H.S. | 43  | Scanty, 10 10 days, 3 months      | +3     | Late estrogenic, 12th day    | 5+ 12th day                    | 5 weeks                         | 600                       | 3+ 18th day                   | Diabetic; fibroid same size after 5 months; operation, intrauterine fibroid; follicle cyst |
| Mrs. R.S. | 44  | Heavy, 14 days, 2 months          | -8     | Cystic hyperplasia, 18th day | 5+ 18th day                    | 3 weeks                         | 1300                      | 3+ 18th day                   | Small fibroid; 3 months after beginning treatment uterus normal size; fibroid not palpable |

was able to tolerate the lactogenic serum at a later time. The hormone is kept under refrigeration of 34 to 36° F.

#### RESULTS OF THERAPY

Twelve patients required only prolactin therapy to regulate excessive menstrual bleeding. Eleven of these were over 40 years of age.

Twenty-two patients received equine gonadotropin therapy after the excessive bleeding had been regulated by prolactin. Only two were over 40 years of age. Four patients became pregnant after the gonadotropin therapy was completed. This would seem to indicate that the antigonad effects of prolactin are temporary and harmless.

Twenty-two patients who had uterine fibromyomata received from 300 to 1300 I.U. of prolactin. All but 5 obtained relief with no further excessive bleeding. This seems important in conjunction with the control of functional bleeding, since it gives evidence that factors other than those now recognized may be responsible for excessive uterine bleeding. It was necessary to do partial hysterectomies for four of these patients and a myomectomy (intrauterine) for the fifth. There was at least one ovarian follicle cyst present in each of the five operative cases.

#### DISCUSSION

If an abnormally large amount of the lactogenic factor of the anterior pituitary exists, there is a disturbance of the control of the anterior pituitary over the normal routine of development of follicle and in corpus luteum, and consequently, of the usual cyclic changes in the endometrium. Estrogen inhibits the production of the lactogenic principle of the anterior pituitary, and conversely the lactogenic hormone inhibits estrogen production in the ovary. On this

basis, it seems rational to suppose that if there is an actual or relative excess of estrogen in the blood, the administration of prolactin should have an antigonadotropic effect in preventing the continued formation of new estrogen by the ovaries. This seems to be borne out by the fact that normally lactating mothers do not ovulate, nor do they menstruate.

The antigonadotropic action of preparations of prolactin was shown in birds by Riddle and Bates (6), and Bates, Lahr, and Riddle (7). Dresel (8), and Lahr and Riddle (9) were able to suppress the estrous cycles in rats with preparations of prolactin. This has been confirmed by Evans, Simpson, and Lyons (10) with purified lactogenic hormone. In the latter experiments, the growth of graafian follicles was suppressed, but the healthy corpora lutea present in the ovary when injections were begun were maintained, and the luteal cells showed the hypertrophy typical of pregnancy or lactation. That the lactogenic hormone induced the luteal cells to form progesterin was shown by Evans, Simpson, and Turpeinen (11). The latter workers, using hypophysectomized and adrenalectomized rats showed that the lactogenic hormone acted upon the persisting luteal tissue causing it to form progesterin as proven by placenta formation. Thus, lactogenic hormone must be considered luteotropic in rats in the sense that it maintains and stimulates to function an already existing, healthy corpus luteum, although large doses of it have never been shown to cause the new formation of luteal tissue as does the proper combination of the other gonadotropic hormones (follicle stimulating and luteinizing factors). In explanation of its follicle-inhibiting action, Bates and Riddle have shown that prolactin inhibits the secretion (or effect) of the follicle-stimulating hormone of the pituitary.

It is possible that the lactogenic hormone may be

considered as acting in two different ways, since patients showing abnormal bleeding due to an insufficiency of progestin might be helped by its luteotropic action, whereas those who are under the influence of a hyper-functional follicular apparatus might conceivably benefit through its inhibiting action on the production of the follicle stimulating hormone

#### CONCLUSIONS

There is an important physiological relationship between the lactogenic factor of the anterior pituitary and the functions of the ovary and endometrium. The lactogenic hormone is antagonistic in its effects.

The use of the lactogenic hormone (prolactin), in a recent series of 34 cases of functional menorrhagia-metrorrhagia has controlled the bleeding successfully in every case.

Equine gonadotropin was used following prolactin for 22 of the 34 patients in order to improve their ovarian function.

Only 5 (23%) patients with uterine fibromyomata required surgery. The other 17 (77%), who had fibroid conditions improved satisfactorily with prolactin treatment only.

Evidence is presented that prolactin has a transitory, harmless effect physiologically, and that there may be other factors partially responsible for excessive uterine bleeding than those which are now recognized.

This method of controlling excessive uterine bleeding, was studied for a period of 4 1/2 years and is reported so that other clinicians may determine the advisability of further investigation of prolactin for the treatment of excessive uterine bleeding.

Grateful acknowledgment is rendered to M. A. Goldzieher and W. R. Lyons for valuable assistance in this investigation.

The equine gonadotropins employed were Gonadin supplied by Cutter Laboratories, Berkeley, Calif., and Anteron, supplied by Schering Corporation, Bloomfield, N. J.

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# Functional Uterine Bleeding

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RICHARDSON (1) defines functional bleeding as that which appears in the absence of gross lesions at unexpected times or in abnormal amounts. The cause is unknown, but it is believed to be due to a dysfunction of one or more of the ovarian or pituitary hormones. It is an extremely bothersome syndrome both to the patient and to the physician. Its frequency and widespread occurrence are well known, and it is therefore of definite interest not only to the gynecologist and endocrinologist, but also to the general practitioner, internist and surgeon.

Its etiologic factors are obscure and the contributions of the experimental laboratory to its pathogenesis have been meager. No true pathological bleeding has been produced experimentally, although many menstrual and pseudomenstrual bleedings have been induced with hormonal agents both in woman and monkey (2).

Functional bleeding may occur from any type of endometrium, cystic and hyperplastic, proliferative, progestational or atrophic. Experimentally, neither the pituitary nor the ovary is essential for uterine bleeding, and Kurzrok (3) believes the responsible factors reside in the endometrium.

Up to recent times, the estrogen withdrawal theory or aberrant estrogenic function has been the basis of all etiological theories. However, it does not explain the bleeding that is clinically noted when continuous large doses of estrogen are given. Also the cystic glandular hyperplasia type, which constitutes probably one-third of all types of functional bleeding, is not satisfactorily explained by an excessive estrogenic supply. Kurzrok (3) points out that neither the blood nor the urine of such patients shows higher estrogenic titers. And furthermore, other tissues supplied by estrogens do not show the effects of overstimulation such as enlargement of the breasts or uterus. Kurzrok therefore feels that it is an endometrial affair, the endometrium taking more than its share of the estrogens and this in turn causing more estrogen to be produced by the ovary. And so the endometrium may be the cause of the cystic follicles frequently found in the ovaries of such patients rather than the cystic follicles causing the hyperendometrium.

The many conflicting theories indicate the cause is unknown. We do know there must be some aberration of function in the ovaries or endometrium or both. No present theory can satisfactorily explain all types of functional bleeding. The factors involved are the endometrial vessels, the endometrium, the ovaries and the pituitary. The intrinsic relationship between these factors is not clearly understood. Indeed little is known of the physiology or hormonal effects of the endometrium itself.

My own view is that all women at some time or other may have some of these functional disturbances during their active sex-endocrine life. In many cases, it is just a temporary phase and if some palliation and regulation can be carried out, nature will readjust her endocrine pattern and she will become 'regular' again. Hamblen (4) says 'normal women may have two to five anovulatory cycles a year. Minor menstrual irregularities are often normal for the individual and only when undesired sterility is related to these irregularities, or when there is a depleting hemorrhage, is therapy justified.'

## ENDOCRINE THERAPY

The use of such endocrine substances as testosterone, chorionic gonadotropin, equine gonadotropin, and a new combination—pituitary gonadotropic substance containing chorionic plus whole pituitary extract—have not yielded successful or desirable results.

### Testosterone

Testosterone undoubtedly will check aberrant bleeding as demonstrated by Mazer and Mazer (5) and by Salmon and his associates (6). The *modus operandi* probably is by its counter depressing activity on the pituitary gland, and the consequent depressed ovarian activity. However, the expense of such therapy is of no little consequence. And more important are the frequent disturbing and embarrassing side effects, as the development of male characteristics such as hirsutism, atrophy of the breasts and change of voice. And, unhappily, not all of these side effects disappear with the discontinuation of treatment. Furthermore, we know it causes atrophic changes to appear in the ovaries and endometrium, and the future endocrine balance may be permanently impaired.

### *Pituitary Gonadotropic Substances*

The pituitary gonadotropic substances theoretically should be a satisfactory type of treatment, because they are supposed to exert trophic influences upon an ovary which for some reason or other is not functioning properly. However, they are the most disappointing form of all endocrine therapy in this field.

#### *Chorionic Gonadotropin*

Chorionic gonadotropin (which is also known as APL pregnancy urine extract, luteinizing substance) has been found sadly lacking in effect in checking and curing functional bleeding. Indeed it has been found wanting in most fields of gynecic endocrinology. And it has even been known to cause ovarian damage through the formation of atretic follicles. Geist (7) and others have found it to be useless in the treatment of abnormal uterine bleeding, and any beneficial effects as reported by some are said to be merely coincidental. Kurzrok (3) uses small blood transfusions in checking functional uterine bleeding. The donor is a pregnant woman in her middle trimester. He feels the value resulting is by reason of the high concentration of pregnancy gonadotropin at this period. But it may very well be due to the high level of estrogens at this time or to some other unknown factor.

#### *Equine Gonadotropin*

Equine gonadotropin (developed from pregnant mare's serum) has experienced a more popular reign, but it is of little or no more value. It is supposedly a potent gonadotropic substance, as evidenced by causing ovulation in experimental animals. Ever since Davis and Koff (8) in 1938 claimed they could produce artificial ovulation in women by means of this hormone, there has been a tremendous volume of this material used throughout the country. Sevringhaus (9) also claimed somewhat similar findings. Hence it was used in many instances of ovarian failure such as sterility, menorrhagias and metrorrhagias, amenorrheas, and even dysmenorrhea.

However, evidence is now accumulating to show that it is very doubtful whether one can ever produce an artificial ovulation or improve ovarian function by this substance. Geist (10) and his associates in a careful analysis of 91 cases followed by observation at laparotomy state they have never seen an ovulation result from its use. Novak and Hofbauer in discussing the above work of Geist's say it is of no proven value and should be discarded. Karnaky gave huge doses to normal women and never observed a change in endometrial pattern. Sexton and Vogt (11) reported only meager results in the treatment of menorrhagia with its use. Erving (12) and his associates found 81 per cent of their cases were unaffected by the use of

equine gonadotropin and in no case was there evidence of stimulation of ovulation. And recently Gray (13) in evaluating equine gonadotropin found it of value in only 50 per cent of his cases of metrorrhagia, a figure easily duplicated by spontaneous cures.

#### *Combined Gonadotropins*

The other gonadotropic substance which is becoming popular at present is the chorionic gonadotropin in combination with a whole pituitary extract synergist.<sup>1</sup> Its commercial name is Synapoidin. In a preliminary report, Mazer and Ravetz (14) claim they arrested dysfunctional bleeding in 14 of 18 patients and evoked menstrual flows in 19 of 23 severely amenorrheic women, some of whom had not menstruated for years, despite all other forms of treatment. Karnaky states he has produced definite changes in endometrial patterns and menstrual changes in normal women. Geist (10) has not found it of much more value than any of the other pituitary hormones.

I have had no experience with its use in the menorrhagias and metrorrhagias, but have used it in a few cases of amenorrhea and sterility. Bleeding has recurred in two amenorrheic women of four so treated. It is too early to determine its value in my sterility cases, although it has not to date changed the anovulatory endometrial pattern of one to that of a normal secretory state. However, I do believe of all the pituitary gonadotropins it is the most promising. But it should be remembered that other substances experienced a similar flurry of popularity. And as Mazer and Ravetz (14) have pointed out, it should be used with care, for serious side effects such as increased size of ovaries and cystic ovaries may result from its indiscriminate use in young girls.

#### *Thyroid*

A discussion of functional uterine bleeding must include a word on the use of thyroid. I think this is by far and large one of the most valuable and most forgotten endocrine substances. There is a tendency to use the newer, fancier and more expensive endocrine products in place of this simple and tested substance. It is of value chiefly in the menorrhagias of the younger age groups. In fact, some believe it is almost specific in these cases. Of course, its value in a true hypothyroid case is unquestioned. But I think it is of inestimable value in the borderline type of case as well. I use it in menorrhagias of the teens and early twenties and in all other cases in which improvement is not rapid or marked in conjunction with other endocrine products. Karnaky uses it to tolerance as a routine measure in conjunction with large doses of diethylstilbestrol.

<sup>1</sup> The combined chorionic and pituitary gonadotropin preparation (Synapoidin) is manufactured by Parke, Davis & Co., Detroit, Mich.



### *Corpus Luteum Hormone*

At one time corpus luteum hormone (progesterin, progesterone), was thought to be the answer for the cure of menorrhagias, because it is supposed to have a quieting effect on the uterus, and it is supposed to be an antagonist to estrin. This thought arose chiefly because most dysfunctional bleedings were of the cystic hyperplastic type, and all were anovulatory, indicating the absence of corpus luteum activity. However, the results were just the opposite as shown by Hamblen (15), Gillman (16) and Zondek and Rozin (17). They showed that progesterone will aggravate a menorrhagia and even cause bleeding in a normal woman in the intracyclic period. However, Weisbader (18) has recently reported that pregneninoline (a synthetic progesterone) has proved effective in checking functional uterine bleeding. He gives large doses, 250 to 350 mg. in divided doses of 50 mg. daily to check the bleeding, and then uses 200 to 240 mg. in divided doses during the second half of the succeeding periods to prevent the recurrence. It is difficult to see the mechanism involved here unless it be by (a) an inhibitory action on the pituitary, (b) an endocrine imbalance causing a relative increase or decrease in the estrogenic level or (c) making the endometrium less refractive to the estrogenic level. On the other hand, Gaines (19) and his associates found pregneninoline of no value in functional uterine bleeding and concluded it had no suppressing effect on the menstrual cycle.

### *The Estrogens*

Theoretically, it would seem that estrogenic substances would aggravate an existing bleeding state because of its proliferative action on the endometrium. However, it is a clinically known fact that estrogens in large doses will check uterine bleeding, either normal or abnormal.

It is obvious that the estrogens play an important rôle in the bleeding mechanism, for even though both ovaries and the pituitary are absent, bleeding can be induced experimentally with estrogens. Furthermore, the absence of estrogens as the result of castration, leads to an atrophic endometrium; the endometrium is atrophic also in the pre-pubescent girl. In pregnancy, during which there is a high estrogenic level, there is a period of physiologic amenorrhea. Apparently there is a level at which gynecic function proceeds normally and cyclically. Karnaky (20) demonstrated an estrogenic hormone bleeding level, above or below which amenorrhea results. This level may vary in different women because of interrelationship with other hormones or because of nervous factors. Karnaky, by giving large doses of estrogenic material, could check abnormal or normal bleeding at will. Upon withdrawal of estrogenic hormone,

the blood level drops until the bleeding level is reached, and uterine bleeding ensues. The bleeding which is clinically noted when continuous doses of estrogenic hormone are given, or in cases in which the ovaries are cystic, is explained by the fact that the hormone fluctuates at the bleeding level, the estrogen being constantly metabolized by liver, kidney and uterus. However, if at any time large doses of estrogen would be given, the bleeding would promptly cease (20).

Up to this point Karnaky has ably explained a most likely theory of bleeding. But the simple elevation of the blood estrogen above the bleeding level cannot explain the permanency of regular menstruation occurring in those women in whom large doses of estrogen have checked the functional bleeding. A temporary benefit in checking the bleeding is obvious, yet Karanky has reported that 87 per cent of his patients, in whom uterine bleeding has been checked with large doses of estrogen, have afterwards had normal menstrual periods. My observations have been the same. The explanation for this phenomenon is apparently the effect of large doses of estrogen on the pituitary, which Karanky failed to discuss. Estrogenic substances are of value in the menopausal patient by virtue of the fact they inhibit the hyperpituitarism which apparently is the cause of the vasomotor imbalance. Large doses of estrogens seem to have a marked contra-physiologic effect on the pituitary gland. This, in turn, will cause a cessation of gonadotropic stimulus to the ovary, and the ovary will, for a period, be inactive. This conclusion is supported by the fact that Karnaky frequently has observed that initially cystic ovaries are no longer so in bleeding patients after large doses of estrogens are given. I have observed smooth ovaries at laparotomy in patients who have received large doses of diethylstilbestrol prior to laparotomy. It is possible that the period of non-activity in the ovary is associated with the regular menstrual periods which follow, since some aberrant ovarian factor may be removed. This idea is substantiated by Friedman's (21) theory that small doses of irradiation to the ovaries of women who have irregular bleeding or amenorrhea are benefited, not because roentgen rays are stimulating, but rather because they may destroy some inhibiting factor in the ovary. He further supports this theory with the fact that Stein and Cohen (22) have treated amenorrhea and sterility by removing surgically the cystic portion of both ovaries. Hence all three of these procedures, a) contraphysiologic estrogen b) irradiation and c) excision of cystic portions of the ovary may remove inhibiting factors in the cystic portion of the ovaries and cause a normal ovarian function to ensue.

Therefore, large doses of estrogens are effective in

checking and curing functional bleeding, by a), raising the estrogenic hormonal blood level above the bleeding level and hence causing an immediate cessation of bleeding, and b) inhibiting the gonadotropic influences of the pituitary and giving the ovary a period of rest, thereby tending to restore permanently normal ovarian function and menstruation.

Clinically, Hamblen (23) and his associates use large doses of estradiol benzoate or some natural estrogen to check uterine bleeding, and follow this with a cyclic treatment consisting of the administration of estrogens in the first half of the cycle and corpus luteum hormone, as progesterone or the synthetic anhydrohydroxy-progesterone, in the second half. By this means they hope, after having checked the bleeding, to maintain an artificial pituitary-ovarian rhythm which will tide the patient over until the normal ovarian pituitary balance occurs. Large doses of progesterone or anhydrohydroxy-progesterone are used, an average of 400 mg. of anhydrohydroxy progesterone per period.

Karnaky (20) checks uterine hemorrhage with large doses of diethylstilbestrol. If bleeding is severe, he injects from 10 to 25 mg. of diethylstilbestrol in oil into the anterior cervix. If bleeding is not severe, he gives the patient 25 5-mg. tablets and instructs them to take one a night for 20 nights. This usually checks the bleeding promptly. The patient then has 5 tablets which are used to control the inevitable withdrawal bleeding which occurs 2 to 8 days after the 20 days of therapy. About 14 to 21 days later, she will experience a normal period and in 87 per cent of his cases the rhythm will again become normal. He also uses thyroid to the point of tolerance, 0.25 to 30 grains daily.

In my experience, a combination of these two methods has proven most successful. Large doses of diethylstilbestrol are used to check the immediate bleeding. This is followed with Hamblen's cyclic treatment, using, however, diethylstilbestrol instead of a natural estrogen, and anhydrohydroxy-progesterone instead of the natural progesterone, to prevent a recurrence of bleeding. Possibly the use of the cyclic therapy to prevent recurrence is unnecessary, as Karnaky suggests, and possibly the progesterone alone is necessary, as Hamblen later used.

I generally prescribe 5 to 10 mg. daily of diethylstilbestrol, depending on the severity of the bleeding, for 15 consecutive days. The patients are advised to take the medication with a glass of milk at night before retiring. This will usually stop the bleeding promptly within 5 to 10 days. Some 5 to 9 days after discontinuing treatment the withdrawal bleeding occurs. This is not to be confused with a regular menstrual period and usually needs no treatment to stop it. Following this, the patient will usually ex-

perience a normal menstrual period some 2 or 3 weeks later. The patient is then instructed to take 2 or 3 mg. of diethylstilbestrol in divided doses from the 10th to the 13th day of the cycle. Beginning on the 14th day the patient takes 10 mg. of anhydrohydroxy-progesterone daily for 10 days. If bleeding ensues before this 10 day period has elapsed, she is instructed to stop the drug. This 100 mg. of anhydrohydroxy-progesterone is less than the accepted amount necessary to produce a progestational endometrium. Thyroid is used when indicated, as previously outlined.

I have recently treated 25 patients by such a regime. In 21 the bleeding was satisfactorily controlled and the patients resumed normal cyclic menstruation. Of these 21, four have since become pregnant within a period of 4 months of the dysfunctional bleeding. Of the 4 patients who failed to respond to treatment bleeding was checked in 2 by curettage, hysterectomies were performed on the other 2. Both of the patients on whom hysterectomies were performed were 40 years of age.

The treatment as outlined above is effective in checking bleeding and regulating menstrual periods. I do not believe it is harmful to the delicate endocrine mechanism of the human female. Gillman (24) has observed massive follicular atresia in baboons given large doses of estradiol benzoate. I have not observed this phenomenon at laparotomy in women following estrogen therapy. The fact that these women experience regular periods after their treatment indicates that no harm is done. Furthermore, it is commonly observed that those women, who are given diethylstilbestrol to inhibit ovulation and so prevent dysmenorrhea in the succeeding period, experience a return of dysmenorrhea as soon as ovulation is not inhibited for that particular month. This would indicate the ovary is not functionally damaged or greatly changed. A complete functional recovery is possible in a certain percentage of cases as is evidenced by the recurrence of a secretory type of endometrium and by subsequent pregnancy. In addition to these advantages, this mode of therapy is inexpensive and oral.

These large doses of diethylstilbestrol may occasionally cause nausea. This can be reduced to a minimum by giving the medication at night with milk. As treatment is continued the nausea frequently disappears. Also, occasionally, it may cause vaginal soreness and backache, but neither of these side effects is as distressing as the prolonged bleeding for which the patient seeks relief.

It should always be remembered that a large proportion of these menstrual irregularities are but passing episodes in the sex endocrine life of a woman. If such patients are aided through these periods, a large percentage will again resume a normal ovarian-

pituitary balance with the consequent menstrual regularity and, perhaps, fertility. Conversely, I believe, if nature, after a few months of artificial therapy, does not take over, then it is not in the power of present-day endocrine therapy to effect a recovery.

#### RADIUM AND RADIATION

I would hesitate to use either radium or roentgen-rays in the treatment of functional uterine bleeding for several reasons. First, even in the smallest doses they have a depressing effect on ovarian activity, and in so treating an already under-functioning ovary, little hope can be held for a satisfactory functional recovery. Secondly, many cases of bothersome bleeding occur in the third and fourth decades, and the results of radiation are notoriously poor in this younger age group. Randall and Lovelady (25) of the Mayo Clinic reported failure in 40 to 50 per cent of the cases in those age groups. Of course, in that group over 40 years of age, treatment with radium or roentgen-rays has a definite place. Thirdly, the dividing line between sub-sterilizing doses and those causing permanent amenorrhea and sterility is so uncertain that not even competent radiologists will guarantee the results. And, lastly, in those women who regain function and later become pregnant, the percentage of abortion is questionably high.

I have had no experience with low-dosage irradiation to the pituitary and ovaries. There have been some glowing reports (26, 27) as to its success. But the fact remains that its usage has not been widespread and we know little of its after effects.

#### CURETTAGE AND HYSTERECTOMY

Curettage should be mentioned. I feel that curettage has a definite place in the treatment of functional uterine bleeding. Briefly, there are a few definite indications for it: a), In those women above the age of 37 in whom a diagnosis of malignancy, polyps or submucous fibroid is always a definite possibility; b), in those women who are bleeding very profusely and for their general condition it is necessary to stop this promptly; c), in those women in whom conservative therapy has failed. I do not believe one curettement, with a dull curette and no strong astringents afterwards, can harm an endometrium and it may yield valuable information. In many instances this may effect a permanent cure. However, repeated curettements or the use of sharp curettes, can produce a scarring and fibrosis of the endometrium; this is to be deplored.

Hysterectomy will be needed in only a very few cases. In my opinion it is preferred to radiation before

the age of 40 as it preserves ovarian function for at least a few years.

#### SUMMARY

An effort has been made to review briefly the present day status of the causes and treatment of functional uterine bleeding. It has been shown that the etiologic factors are obscure. Such endocrine substances as testosterone, progesterone and the numerous gonadotropins have been unsatisfactory or undesirable as therapeutic measures for the several reasons stated. The author believes that thyroid is of considerable therapeutic value, although it has been recently underestimated. On the basis of the estrogenic theory of uterine bleeding, diethylstilbestrol has been used in large doses to check immediate bleeding, followed by cyclic diethylstilbestrol and anhydrohydroxy-progesterone therapy to prevent a recurrence. The result of this type of therapy in 25 cases is presented. Radiation, frequent curettage and hysterectomy should play a minor role in the therapy of functional uterine bleeding.

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# Comparative Clinical Effects of Orally Administered Alpha-Estradiol and Diethylstilbestrol on Postpartum Engorgement of the Breast

## [[Comparative Action of Estrogens]]

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ORAL DOSES of other estrogens comparable to those of diethylstilbestrol have not been employed extensively because of the expense involved or the difficulty in obtaining a non toxic solvent that would insure efficient absorption. Since previous experience with diethylstilbestrol has established a measuring stick for evaluating estrogenic activity, a series of 156 puerperal women have been given diethylstilbestrol or  $\alpha$  estradiol and the effects on breast engorgement compared.

### PROCEDURE

The relative effectiveness of orally administered  $\alpha$  estradiol and diethylstilbestrol on breast engorgement was ascertained, respectively, in 61 and 95 women, 79 of the latter number were included in a previous report (1). In addition the results were compared with conditions in 75 women who received no medication. Approximately 60 per cent of each group were primipara. The age range was from 14 to 48 years with the majority under 30 and only two were 40 years or older. Therapy was begun within the first 36 hours post partum and in all but 10 within 24 hours. In the majority of instances  $\alpha$  estradiol was administered at regular intervals day and night for 4 days, while diethylstilbestrol was usually given once daily for 1 to 6 days. The former was dissolved in propylene glycol and placed under the tongue. The patient was requested to lie with the head turned to one side and cautioned not to swallow for five minutes. Originally the propylene glycol contained 0.5 mg of

$\alpha$  estradiol per cc, but it was soon learned that larger doses were required. This necessitated giving so much of the solution that it ran down the throat where it was probably not absorbed or was destroyed or inactivated in the stomach. Subsequently this difficulty was largely eliminated by employing a solution containing 5 mg per cc. Diethylstilbestrol was given either in enteric coated or uncoated tablets.

Medication was given to patients who preferred not to nurse their children or who had stillbirths, without further selection.

### RESULTS

In a previous study (1) it was noted that breast engorgement could usually be inhibited if diethylstilbestrol was given within the first 24 hours post partum and continued for 4 or 5 days. Tables 1 and 2

TABLE 1 RESULTS OF ORALLY ADMINISTERED ALPHA ESTRADIOL ON BREAST ENGORGEMENT

| Number of Cases | Dosage in Milligrams |            | Results |      |         |          |
|-----------------|----------------------|------------|---------|------|---------|----------|
|                 | Daily                | Total      | Good    | Fair | Failure |          |
|                 |                      |            |         |      | Number  | Per cent |
| 13              | 0.75 to 0.17 t i d   | 8.5 to 2.1 | 1       | 2    | 10      | 77       |
| 10              | 0.75 to 0.17 q 6 hr  | 7.5 to 1.8 | 1       | 7    | 2       | 20       |
| 13              | 1.7 q 4 hr           | 45 to 30   | 7       | 5    | 1       | 7.7      |
| 12              | 1.7 q 6 hr           | 30         | 3       | 8    | 1       | 8.5      |
| 13              | 2.5 q 6 hr           | 40         | 11      | 2    | 0       | 0.0      |
| Totals 61       |                      |            | 23      | 24   | 14      | 22.9     |

TABLE 2. RESULTS OF ORALLY ADMINISTERED DIETHYLSTILBESTROL ON BREAST ENGORGEMENT

| Number of Cases | Dosage in Milligrams      |          | Results |      |         |          |
|-----------------|---------------------------|----------|---------|------|---------|----------|
|                 | Daily                     | Total    | Good    | Fair | Failure |          |
|                 |                           |          |         |      | Num-ber | Per-cent |
| 41              | 5 q.d.                    | 5        | 24      | 13   | 4       | 9.8      |
| 15              | 10 q.d.                   | 20 to 10 | 6       | 3    | 6       | 40.0     |
| 22              | 10 to 5 q.d.<br>or b.i.d. | 35 to 25 | 15      | 6    | 1       | 4.5      |
| 17              | 10 q.d.                   | 50 to 40 | 15      | 2    | 0       | 0.0      |
| Totals 95       |                           |          | 60      | 24   | 11      | 16.6     |

indicate that  $\alpha$ -estradiol produced effects comparable to those of diethylstilbestrol when the larger doses were employed, but there was a higher percentage of failures with small doses of  $\alpha$ -estradiol. Previous experience revealed that frequent daily doses of diethylstilbestrol did not increase appreciably the effectiveness of the drug. On the other hand,  $\alpha$ -estradiol in divided doses at short intervals was more effective than a single daily dose of the same magnitude. The less favorable results obtained with 20 to 10 mg. of diethylstilbestrol followed the use of non-coated tablets. This suggests partial destruction or inactivation of the drug in the stomach.

Among the mothers receiving at least 40 mg. of either drug, none had breast engorgement. By contrast, mastalgia appeared in 97 per cent (73 of 75 cases) of those not treated.

A 'fair' result indicates discomfort for 12 hours or less, while a 'failure' denotes that symptoms persisted 24 to 72 hours. Among the untreated group, the period of painful engorgement averaged 36 hours.

Lactation was usually diminished or delayed, but was never prevented entirely by either drug.

Salmon et al. (2) did not describe toxic effects, including nausea and vomiting, from the use of  $\alpha$ -estradiol. The authors also observed no undesirable reactions.

SUMMARY AND CONCLUSIONS

Sixty-one postpartum women were given  $\alpha$ -estradiol in propylene glycol sublingually to test the effect on breast engorgement as compared with that produced by diethylstilbestrol. Comparable total dosages of both drugs given over the same period effected similar results provided the  $\alpha$ -estradiol was administered in divided doses at regular intervals throughout the day and night as contrasted to the same quantity of diethylstilbestrol employed once daily. Initiation of lactation was usually delayed, but not inhibited entirely. Toxic effects were not observed.

The use of  $\alpha$ -estradiol has certain disadvantages, as compared with diethylstilbestrol, such as the need to give medication frequently, and the greater expense of the drug.

The diethylstilbestrol was supplied through the courtesy of Dr. J. A. Morrell of E. R. Squibb and Son, New Brunswick, N. J. The  $\alpha$ -estradiol was supplied by Dr. Edward Henderson of the Schering Corporation, Bloomfield, N. J.

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# Effect of Estrogenic Therapy on Decubitus Ulcers of a Large Rectocele

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MANY AUTHORS have demonstrated the effect of estrogens upon the vaginal epithelium. Papanicolaou and Shorr (1) have noted a proliferation of the vaginal epithelium of menopausal patients receiving estrogenic therapy, by examining vaginal smears. Geist and Salmon (2) have correlated the alterations in the vaginal smears with histological studies of the vaginal mucosa. On the basis of these

## CASE REPORT

Mrs L O, 27 years of age, was referred for gynecological opinion on Oct 11, 1940, with a protrusion at the vulva and a history of vaginal staining of 6 months duration. The primary condition for which she was hospitalized was rheumatic cardiac disease with decompensation. She had had two difficult operative deliveries 6 and 4 years ago. Her last menstrual period occurred 2 years ago.



Fig 1 HUGE RECTOCELE WITH ULCERATIONS AND ATROPHY OF THE MUCOSA BEFORE ESTROGENIC THERAPY

Fig 2 APPEARANCE OF THE VAGINAL MUCOSA, SHOWING COMPLETE HEALING OF ULCERATIONS, 7 WEEKS AFTER ESTROGENIC THERAPY WAS BEGUN

changes, Schockert (3) and many others advocated intramuscular injections of estrogenic substances for the treatment of atrophy of the vulva and vagina. Clafien (4) found the estrogens to be effective when administered locally. Later, Mishell and Motyloff (5), and Finkler and Antopol (6) obtained favorable results with the local application of estrogenic ointment in cases of senile vulvo vaginitis.

The following case illustrates the effect of estrogens upon decubitus ulcers of a huge rectocele in a young woman with prolonged amenorrhea.

Pelvic examination revealed a huge rectocele about 10 cm in diameter protruding through the introitus. On the surface were two irregular ulcerations, each about 3 cm in length, and 1 cm in width. The mucosa of the rectocele was inflamed, atrophic, and fissured (fig 1). The cervix was found behind the symphysis. The uterus was normal in size and retroverted. The adnexae were not palpated.

For two months the patient was treated with bed rest, topical applications of silver nitrate to the vaginal ulcerations and vaginal packing with vaseline gauze to support the rectocele. There was no appreciable improvement during this time.

Estrogenic therapy was begun Dec 12, 1940. An injec-

tion of 2,000 R.U. of estradiol benzoate<sup>1</sup> was given three times a week for a month. In addition, 2,000 I.U. of estrogen in ointment form<sup>1</sup> was applied locally every other day for three treatments. During the second week a daily application of 2,000 I.U. was similarly given. A daily dosage of 5,000 I.U. of estrogen was applied to the vaginal ulcerations and mucosa during the third and fourth weeks. After each local treatment the rectocele was replaced in the vagina and held there with vaseline gauze.

Within a week the ulcerations were healing by epithelialization and the mucosa appeared thicker and less fissured. On Jan. 17, 1941, five weeks after estrogenic therapy was begun, the ulcerations were found to be completely healed. The vaginal mucosa appeared normal and there was a marked decrease in the size of the rectocele. A photograph taken Feb. 3, 1941, illustrates the improvement (fig. 2). Simultaneously, the patient was treated medically for cardiac decompensation, and a decrease in the ascites and edema resulted. When last seen, Nov. 28, 1941, the vaginal mucosa of this patient was entirely intact and normal in appearance.

<sup>1</sup> The estrogenic preparations (Dimenformon benzoate ampoules and Menformon dosules) were supplied by Roche-Organon, Inc., Nutley, N. J.

#### CONCLUSIONS

This case illustrates the healing effect of estrogenic substances on ulcerations and atrophy of the vaginal mucosa of a huge rectocele in a young cardiac patient with amenorrhea of 2 years duration.

We feel that rest in bed, replacement of the rectocele and improvement in the cardiac status, with diminution of the ascites and edema, undoubtedly played an important rôle in the healing of the vaginal ulcers. Nevertheless, estrogenic therapy, with its proliferative effect on the vaginal mucosa, unquestionably hastened healing. Estrogenic therapy may be utilized for hastening the healing of mucosal ulcers of cystoceles, rectoceles and uterine prolapse in preparation for operation.

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# Studies on the Etiology of Human Breast Disease

## I. Urinary Excretion of Follicle-Stimulating Hormone, Estrogens and 17-Ketosteroids in Adolescent Mastitis of Males<sup>1</sup>

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## [Adolescent Mastitis]

ADOLESCENT or puberty mastitis in the male is akin to that normally seen at the onset of breast development in young girls. In the male it usually appears between the 12th and 16th year. It is characterized by the presence of a well defined, freely movable discoid or round palpable mass of breast tissue, closely associated with the areola. The mass may vary in size from less than 1 centimeter to 5, but as a rule is 2 to 3 centimeters. The overlying areola and nipple may be enlarged. Tenderness is not uncommon and may be the first and only sign noted by the patient. The process is usually unilateral at the onset, but may affect both breasts simultaneously or successively. Adolescent mastitis must be distinguished from gynecomastia in which the size, contour and elements approach that of the normal adult female breast, and from enlargement of the breast due entirely to adipose tissue such as is seen frequently in adiposo genital dystrophy and in eunuchs.

Adolescent mastitis in the male occurs more commonly than is generally recognized. Jung and Shafston (1) in approximately 1000 examinations found that the appearance of a palpable mass of mammary tissue is an integral part of the process of puberty. It is not seen more often because of the frequently transient character of the process, which may arise and regress within even a month. The cases which are usually seen by physicians are those in whom growth is rapid, tenderness is marked, or the duration is prolonged. These lesions occur at a time when sexual metamorphosis is relatively rapid as a result of hormonal stimulation (2). It seemed possible therefore

that a temporary imbalance of various endocrine factors might be responsible and that this might be reflected in the excretion rates of the sex hormones and their end products. Consequently a study of the urinary excretion rates of the follicle stimulating hormone of the anterior hypophysis (FSH) as well as of estrogens and 17 ketosteroids was carried out. There were 21 subjects, ranging in age from 12 to 16 years, who entered the clinic for examination because of disturbances of the breast. In many instances it was not possible to obtain more than one 24-hour specimen for assay. Although frequent titrations are not as necessary in boys as in girls (2) it would have been desirable to have more determinations, especially since spontaneous regression was common in this series. The findings in these cases were compared with a large series of assays, which were made on normal boys and girls in the same age range (2).

### *Technique of Extraction and Assay of the Hormones*

Follicle stimulating hormone, prolan A, gonadotropic hormone (FSH) was precipitated from the urine by means of ethyl alcohol, using the original method of Asheim and Zondek. Assay was carried out on inbred immature pure strain female mice (Bar Harbor C 57) between 19 and 21 days old and weighing between 6 and 8 grams. Vaginal opening was used as the criterion of gonadotropic activity in the extract. This type of end point is perhaps not as sensitive as that of follicle stimulation or that of increased ovarian or uterine weight. It was chosen purposely, however, so that a positive response would indicate a significant elevation. In the earlier work the urine was so concentrated as to detect a minimum of 80 mouse units (M.U.) per 24 hours. This level proved

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<sup>1</sup> This is paper No. 555 of the Cancer Commission of Harvard University.



TABLE 1. SEX HORMONE EXCRETION LEVELS IN ADOLESCENT MASTITIS.

| Patients |             |                |                      |              | Values in Normal Individuals    |       |                                       |       |                                  |        |                                       |        |
|----------|-------------|----------------|----------------------|--------------|---------------------------------|-------|---------------------------------------|-------|----------------------------------|--------|---------------------------------------|--------|
|          |             |                |                      |              | Males                           |       |                                       |       | Females                          |        |                                       |        |
| Name     | Age         | Estro-<br>gens | 17-Keto-<br>steroids | FSH          | Estrogen, i.u.<br>Average Range |       | 17-Ketosteroids, mg.<br>Average Range |       | Estrogens, i.u.<br>Average Range |        | 17-Ketosteroids, mg.<br>Average Range |        |
| E.F.     | years<br>12 | i.u.<br>54     | mg.<br>6.0           | M.U.<br>N.D. | 30                              | 10-60 | 13.0                                  | 9-15  | 240                              | 30-400 | 10.2                                  | 6-13.2 |
| P.M.     | 12          | 144            | 8.5                  | N.D.         |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 172            | 9.0                  | >25          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 202            | 10.0                 | N.D.         |                                 |       |                                       |       |                                  |        |                                       |        |
| A.S.     | 12          | 48             | 7.6                  | <80          |                                 |       |                                       |       |                                  |        |                                       |        |
| T.M.     | 12          | 40             | 6.0                  | <35          | 40                              | 20-80 | 15.0                                  | 10-19 | 380                              | 50-600 | 11.4                                  | 6-15.0 |
|          |             | 50             | 6.5                  | <60          |                                 |       |                                       |       |                                  |        |                                       |        |
| F.P.     | 12          | 10             | 13.8                 | N.D.         |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 21             | 14.4                 | N.D.         |                                 |       |                                       |       |                                  |        |                                       |        |
| A.S.     | 12          | 100            | 9.9                  | >40          |                                 |       |                                       |       |                                  |        |                                       |        |
| S.D.     | 13          | 96             | 15.6                 | <80          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 72             | 16.0                 | <80          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 178            | 13.2                 | <30          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 248            | 25.2 <sup>1</sup>    | <30          |                                 |       |                                       |       |                                  |        |                                       |        |
| T.C.     | 14          | 204            | 6.5                  | <20          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 124            | 8.8                  | <25          |                                 |       |                                       |       |                                  |        |                                       |        |
| M.B.     | 14          | 200            | 12.0                 | <25          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 50             | 11.8                 | N.D.         |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 190            | 16.0                 | <25          |                                 |       |                                       |       |                                  |        |                                       |        |
| N.P.     | 14          | 48             | 7.2                  | <80          |                                 |       |                                       |       |                                  |        |                                       |        |
| H.C.     | 14          | 18             | 10.0                 | <20          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 105            | 8.4                  | >30          |                                 |       |                                       |       |                                  |        |                                       |        |
| R.B.     | 14          | 48             | 6.6                  | <40          |                                 |       |                                       |       |                                  |        |                                       |        |
| H.S.     | 14          | 15             | 9.5                  | <40          |                                 |       |                                       |       |                                  |        |                                       |        |
| G.G.     | 14          | 92             | 19.5                 | >95          |                                 |       |                                       |       |                                  |        |                                       |        |
| M.A.     | 15          | 74             | 14.4                 | <50          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 20             | 13.5                 | <80          |                                 |       |                                       |       |                                  |        |                                       |        |
| W.H.     | 15          | 30             | 9.0                  | <20          |                                 |       |                                       |       |                                  |        |                                       |        |
| T.M.     | 15          | 90             | 9.0                  | N.D.         |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 60             | 6.9                  | N.D.         |                                 |       |                                       |       |                                  |        |                                       |        |
| L.C.     | 15          | 105            | 14.3                 | 26           |                                 |       |                                       |       |                                  |        |                                       |        |
| P.H.     | 16          | 20             | 16.0                 | <80          |                                 |       |                                       |       |                                  |        |                                       |        |
| I.A.     | 16          | 30             | 14.4                 | <20          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 430            | 13.0                 | <25          |                                 |       |                                       |       |                                  |        |                                       |        |
|          |             | 192            | 19.8 <sup>1</sup>    | >60          |                                 |       |                                       |       |                                  |        |                                       |        |
| H.H.     | 16          | 160            | 13.5                 | N.D.         |                                 |       |                                       |       |                                  |        |                                       |        |

<sup>1</sup> On treatment with testosterone propionate.  
N.D., not determined.

to be too high to detect its presence in most cases. Later on, therefore, the minimal level tested was between 20 and 40 m.u. One mouse unit is defined as the minimal amount of material which, when in-

jected in five equal parts over a period of 48 hours, will produce vaginal opening in the animals 96 hours after the first injection.

*Estrogens and 17-ketosteroids.* The urinary estrogens

and 17 ketosteroids were extracted by the method of Smith and Smith (3). This consists of preliminary hydrolysis with hydrochloric acid and subsequent extraction with benzol in a continuous extractor. The estrogens were separated from the 17 ketosteroids, using in principle the method of Gallagher et al (4). With this technic the 17 ketosteroids, which are insoluble in alkali, remain in the neutral fraction and are thus separated from the phenolic estrogens which are soluble in alkali (NaOH). The crude total estrogens and 17 ketosteroids were assayed without further purification.

The estrogens were assayed on inbred pure strain ovariectomized mice (Bar Harbor C 57) or rats (Slonaker) with a minor modification of the Allen Doisy method. Estrogens are expressed as international units equivalent in biological activity to crystalline estrone.<sup>2</sup>

The 17 ketosteroids were measured colorimetrically. We have used this method to estimate the androgenic activity in the urine. The 17 ketosteroids include the androgens, such as androsterone, and dehydroisandrosterone and also closely related compounds which are not androgenic in biological activity when they are excreted, but many represent catabolic changes of such compounds. The development of the color for titration was essentially that described by Oesting (5), except that certain conditions such as temperature, light and purity of reagent were kept as uniform as possible. The reaction which was originally described by Zimmerman (6) is based on the ability of meta dinitrobenzene to produce a color reaction quantitatively with substances containing the  $\text{CH}_2\text{CO}$  grouping in alkaline alcoholic solution. Readings were made on the Evelyn photoelectric colorimeter and the values are expressed in terms of milligrams equivalent to that of crystalline androsterone.<sup>3</sup>

#### RESULTS

The levels of hormonal excretion are given in table 1. They represent three different groups: a) The values obtained in the groups under consideration. b) Average values and range of values for boys of the same chronological age. c) Average values and range of values for girls of the same chronological age.

<sup>2</sup> Crystalline estrone was supplied for standardization through the courtesy of Dr. E. A. Sharpe, Parke Davis & Co., Detroit, Mich.

<sup>3</sup> The values which represent the crude total levels for 17 ketosteroids cannot be compared to those of other writers. This is due to the fact that the methods of titration and extraction in different laboratories are not the same.

curves was supplied through the courtesy of Dr. Ernst Oppenheimer of Ciba Pharmaceutical Products, Inc., Summit, New Jersey and Dr. Erwin Schwenk of the Schering Corporation, Bloomfield, N. J.

#### DISCUSSION

The results indicate that in most of the cases there was an abnormality in the urinary excretion rate of either the estrogens, the 17 ketosteroids or both when compared with the normal controls. The 17 ketosteroid excretion was frequently below, or at the lower limits of the average range, whereas the estrogen excretion was significantly elevated in almost one-half of the patients. When each case is considered individually it can be seen that some have both a lowered 17 ketosteroid and an elevated estrogen excretion, while others display only an abnormal estrogen or depressed 17 ketosteroid output. A few of the patients had normal rates for both types of hormones. It seems, therefore, that there is no consistent pattern of excretion if only a single type of hormone is considered. However, consideration of the ratio of the 17 ketosteroids to the estrogens seems to clarify the situation. In the patients who have atypical excretion rates of one or both of the hormonal groups there is a definite shift of the ratio toward the feminine type, i.e., estrogen levels out of normal proportion to the 17 ketosteroid levels. This is most obvious in those individuals in whom the estrogens were elevated in the presence of lowered 17 ketosteroids. The significance of the shift in ratio is shown clearly in the tables by comparison of the levels of the patients studied with normal boys and girls of the same chronological age. It is interesting to note that in many instances the excretion rates of the boys with mastitis fall into the same range as those of girls of the same age. Since girls mature somewhat earlier than boys such a comparison may not be strictly analogous, but the trend is demonstrated.

It is true that in some of the cases, the levels for both the 17 ketosteroids and estrogens were within the average range. This is difficult to explain in the light of the other findings. Nevertheless, there are several possibilities: a) The process may be sufficiently advanced or of such long duration, that in spite of normal levels at the time of assay, the lesion is irreversible and therefore falls into the groups which are seen for the first time in later life. b) The assays may have been made after the exciting factors have returned to normal, i.e., regression of the lesion was taking place when the determinations were made. As far as can be ascertained on such a small group, there is no direct correlation between the duration of symptoms, speed of regression and the values obtained.

Assays for FSH were made in an effort to detect hyperactivity of the anterior pituitary gland. In several cases an elevated level was found, but even though this may be suggestive of hyperactivity, the data were too few to be of significance. This is espe-

cially true since males of this age group may show elevated values without puberty mastitis (2). An increase in FSH may be an index of the activity of other pituitary hormones such as the poorly understood mammogenic hormone, which is a possible etiological factor.

From the data presented it appears that adolescent mastitis in males occurs in the presence of a hormonal imbalance in which the influence of the estrogens plays an important rôle. Analogous lesions can be produced in male rodents and likewise in the human male with estrogenic hormone (7). Several observers have reported similar changes after the administration of testosterone (8, 9). The possibilities involved are beyond the scope of this paper. Similar studies on gynecomastia in young men and on chronic mastitis in older males will be published in the near future in an effort to further clarify these changes.

#### CONCLUSIONS

Adolescent mastitis in males appears to be associated in many instances with atypical urinary excretion rates of the estrogens and 17-ketosteroids,

probably as a result of sexual metamorphosis. The syndrome is more closely related to the ratio of excretion between the 17-ketosteroids and estrogens, rather than to individual rates. The rôle of the anterior pituitary gland is uncertain.

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# Testosterone Propionate Pellet Absorption in the Female

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THE CURRENT LITERATURE contains several reports on the rate of absorption of pellets of sex steroids implanted in experimental animals (1, 2). In the human being, however, only scant data are available that may furnish adequate information as to dosage and length of duration of effects of sex steroids used in this manner. No information is available as to the fate of androgenic pellets in the human female. The primary object of this article is to report our collected data on the rate of absorption of pellets of testosterone propionate implanted in patients with various gynecic disorders.

## MATERIAL AND METHODS

**Implantation of pellets.** All implantations were made under sterile conditions in the operating room. The skin of the abdomen was prepared and then an area approximately 3 cm. in length between the pubis and umbilicus was infiltrated with 1 per cent procaine down the midline to the rectus sheath. An incision was made through the skin, subcutaneous fat and the rectus sheath was visualized. A small incision was made in the sheath exposing the rectus muscle. The pellet, or pellets, were then inserted under the sheath to lie on top of the muscle belly. The fascial sheath was closed with #1 chromic catgut and the skin and subcutaneous fat approximated by silk stay sutures. The whole procedure was frequently performed in 7 to 10 minutes. At the beginning of the study of this problem (3) the thigh was used but this site was abandoned because pain on walking frequently persisted for a few weeks.

The data on the rate of absorption were obtained by the use of pure crystalline testosterone propionate pellets that were machine made under aseptic conditions and supplied by one manufacturer.<sup>1</sup> The pellets used were of two shapes, viz. cylindrical and pill shaped, and they varied in weight from 22 to 200 mg. They were smooth, somewhat glossy in appear-

## [Androgens in Gynecology]

ance and of approximately the same density. On recovery, the pellets showed slight roughening of the surface and a more or less uniform shrinkage in the original shape (fig. 1). The pellets were implanted subfascially on the muscle belly in order to assure better blood supply, more uniform rates of absorption and to lessen the tendency to be expelled spontaneously.

Sixty seven implantations were performed on 63 patients without untoward effects. Sixty patients in this series had but one implantation of 1 to 4 pellets. One patient had three implantations and two had two implantations. A total of 123 pellets were used. Of this number, 23 pellets became available for the study of absorption rates. Fifteen pellets were removed surgically in 8 patients, thus affording an opportunity to study the rate of absorption and tissue



Fig. 1 a) FOUR SMALL PELLETS ORIGINALLY WEIGHING FROM 23-25 MG., implanted 133 days previously, (case 12 table 1), b) FOUR PELLETS ORIGINALLY WEIGHING 103 MG. EACH, implanted 175 days previously, (case 5 table 1)

reaction about the pellets. Eight pellets were salvaged from the 17 pellets that were spontaneously expelled in 9 patients. It is interesting to note that about 14 per cent of the pellets sloughed out. Pellets sloughed as early as 10 days and as late as 104 days. This phenomenon may have been a response on the part of the host as a reaction to a foreign body. However, faulty technique may have been responsible. This may be adduced from the fact that reimplantation in 2 patients in whom sloughing of pellets had previously occurred was not followed by a similar sequence.

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<sup>1</sup> The pellets of testosterone propionate were supplied through the courtesy of Dr. E. Oppenheimer and Dr. R. MacBrayer of Ciba Pharmaceutical Products Inc., Summit, N. J.

TABLE I. TESTOSTERONE PROPIONATE PELLET ABSORPTION IN THE FEMALE

| Patient         | Thera-<br>peutically<br>Effective | Weight<br>of<br>Pellet<br>mg. | Weight of<br>Recovered<br>Pellet<br>mg. | Days in Situ     | Average<br>Absorption<br>per Day,<br>mg. | Diagnosis                                |
|-----------------|-----------------------------------|-------------------------------|---|------------------|--|--|
| 1               | Yes                               | 200.0                         | 142.5                                   | 56               | 1.03                                     | Menorrhagia and fibromyoma               |
| 2               | Yes                               | 101.4                         | 25.5                                    | 177              | 0.43                                     | Nocturia and fibromyoma                  |
| 3               | Yes                               | 101.6                         | 43.8                                    | 84 <sup>1</sup>  | 0.69                                     | Menorrhagia, metrorrhagia                |
| 4               | Yes                               | 101.8                         | 39.1                                    | 136              | 0.46                                     | Menorrhagia and fibromyoma               |
| 5               | Yes                               | 103.0                         | 29.6                                    | 175              | 0.42                                     | Menopausal syndrome                      |
|                 |                                   | 103.0                         | 34.4                                    | 175              | 0.38                                     |  |
|                 |                                   | 103.0                         | 35.3                                    | 175              | 0.38                                     |  |
|                 |                                   | 103.0                         | 35.6                                    | 175              | 0.37                                     |  |
| 6               | Yes                               | 101.8                         | 49.0                                    | 104 <sup>1</sup> | 0.51                                     | Menorrhagia and fibromyoma               |
| 7               | No                                | 102.8                         | 50.1                                    | 170              | 0.31                                     | Dysmenorrhea                             |
|                 |                                   | 51.2                          | 15.4                                    | 170              | 0.21                                     |  |
| 8               | Yes                               | 102.2                         | 69.5                                    | 36 <sup>1</sup>  | 0.90                                     | Dysmenorrhea                             |
|                 |                                   | 51.8                          | 31.8                                    | 36 <sup>1</sup>  | 0.56                                     |  |
|                 |                                   | 51.2                          | 29.5                                    | 36 <sup>1</sup>  | 0.60                                     |  |
| 9               | No                                | 47.0                          | 37.2                                    | 38               | 0.26                                     | Massive fibromyoma                       |
| 10              | No                                | 50.0                          | 48.6                                    | 3                | 0.47                                     | Massive fibromyoma                       |
| 11 <sup>2</sup> | No                                | 50.0                          | 35.3                                    | 38 <sup>1</sup>  | 0.46                                     | Menorrhagia, metrorrhagia and fibromyoma |
|                 |                                   | 50.0                          | 32.4                                    | 45 <sup>2</sup>  | 0.37                                     |  |
| 12 <sup>2</sup> | No                                | 23.0                          | 5.2                                     | 133              | 0.13                                     | Menorrhagia, metrorrhagia and fibromyoma |
|                 |                                   | 23.4                          | 5.4                                     | 133              | 0.14                                     |  |
|                 |                                   | 23.6                          | 5.7                                     | 133              | 0.14                                     |  |
|                 |                                   | 25.0                          | 7.7                                     | 133              | 0.13                                     |  |
| 13              | Yes                               | 23.6                          | 11.4                                    | 59 <sup>1</sup>  | 0.23                                     | Menorrhagia and fibromyoma               |

<sup>1</sup> Pellet spontaneously expelled.  
<sup>2</sup> 11 and 12, implantation in the same patient on two different occasions.

RESULTS

Since there seemed to be no significant difference in the absorption rates of the pellets that were surgically removed and those that sloughed, the data on both are included in this report. This observation confirms a similar impression held by Howard and Jewett (4). Table 1 records the number of days the pellets remained in situ, the original weight of the pellets, the weight of the pellets recovered, and the average absorption per day. In figure 2 the percentage of absorption of 10 pellets of roughly 100 mg. each is plotted against the number of days that the pellets remained in situ. Figure 3 shows the mean curves of percentage absorption for each weight-group of pellets, i.e. five 25-mg. pellets, seven 50-mg. pellets, one 200-mg. pellet, and ten 100-mg. pellets. Note that the distribution for each group allows for a mean curve of

similar character. From the graphic analysis of these absorption curves it appears that the relative absorption over a given period of time is less the larger the size and weight of the pellet although the absolute absorption is greater. This is of significance for the interpretation is clear. If pellets are manufactured under standard conditions i.e. uniformly compressed crystalline material, it holds that pellets of greater weight will be of proportionately greater size. The rate of absorption per pellet will, therefore, depend on its weight, size and surface area. The percentage of absorption of each weight group of pellets will follow its own definite curve. The total rate of absorption on any given day or at any given time depends on the number of pellets implanted and not on the actual

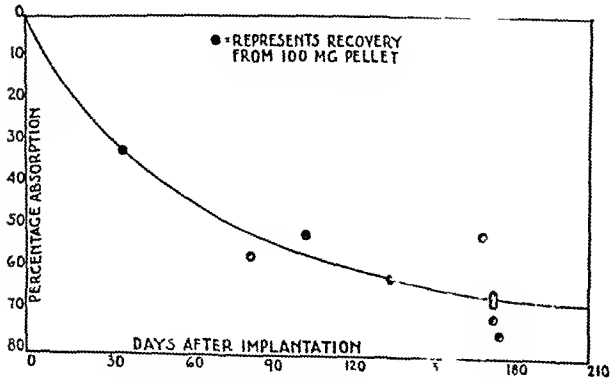


Fig. 2. PERCENTAGE MEAN ABSORPTION CURVE FOR 100 MG. PELLETS

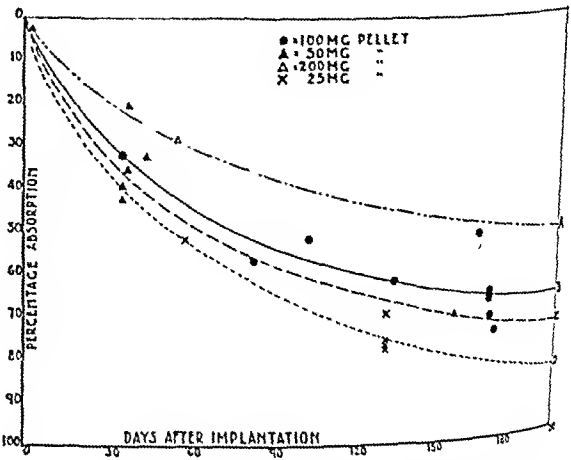


Fig. 3. PERCENTAGE MEAN ABSORPTION CURVES FOR A, 200 mg., B, 100 mg., C, 50 mg., D, 25-mg. pellets

weight of the pellets. For instance, in case 7, a 100 mg. and a 50-mg. pellet were implanted at one time. During the 170 days that they remained in situ, it may be said that an average of 0.520 mg. of testosterone propionate was given off per day by the two pellets. Actually, the 100-mg. pellet gave off only 50 per cent more material than the 50-mg. pellet and not twice as much as would be expected if the rate of absorption depended merely on weight. If three 50-mg. pellets had been implanted instead of the 100 and the 50-mg. pellets then the average daily absorption would probably have been about 0.63 mg. in that particular patient. In other words, 150 mg. composed of three separate 50-mg. pellets implanted at one time would have given off more particles of material at the end of 170 days than 150 mg. composed of one 100 and one 50-mg. pellet, or as much as 200 mg. composed of two 100-mg. pellets. Such an assumption is again borne out by an analysis of case 8 in which one 100 and two 50-mg. pellets were implanted at one time. Since pellets of similar size are more or less absorbed at moderately uniform rates (see case 5 and case 12) and since the rate of absorption depends on the number of pellets and their surface area we undertake to present the following hypothesis: The rate of absorption of any given amount of crystalline hormone depends on the number of pellets implanted at one time and not on the size or weight of the pellets and the time that the pellets continue to give off appreciable material depends on the size and weights of the pellets implanted.

Probably the most important factors in the rate of absorption are the surface area of the pellet exposed to the action of the body fluids, the density of the pellet, the size of the particles (crystals) and the site of implantation. Howard and Jewett found that for the first few days after pellet implantation there was a rapid absorption amounting to 3 or more milligrams per day when using 200-mg. pellets. After this they believed that capsule formation about the pellet slowed the absorption rate to somewhere between 0.5 mg. to 1.0 mg. per day (4). They implanted their pellets subcutaneously. In our series, capsule formation was an inconstant feature, probably because of the site of implantation. Forbes emphasizes that the site of implantation (e.g. intramuscular instead of subcutaneous) may considerably alter the absolute periods required for absorption of a pellet. Mark and Biskind (5) in their work on rats found that the physiological need of the animal plays no rôle in the rate of absorption since there was no significant difference in the rate of absorption of pellets implanted in either castrate or intact animals. Forbes found that the sex of rats had no differential effect

on absorption rates. The values obtained by us for absorption rates of testosterone propionate pellets implanted in females were more or less in agreement with the values obtained for men by other investigators.

#### SUMMARY AND CONCLUSIONS

1. Pellets of testosterone propionate implanted subfascially for the therapy of certain gynecic disorders proved, with certain reservations, to be a satisfactory method of administering small amounts of the hormone over a prolonged period of time without provoking arrhenomimetic phenomena.

2. Data on the average absorption rate per day were obtained on 23 pellets in 13 instances. The number of days the pellets remained in situ varied from 3 to 177 days.

3. The weight of the pellets in this series fell into four groups: a), approximately 25 mg. (5 pellets); b), 50 mg. (7 pellets); c), 100 mg. (10 pellets); d), 200 mg. (one pellet). When the percentage of absorption was plotted against the number of days that the pellets remained in situ, the resultant curves were more or less smooth with the individual deviations of each weight-group being only moderate in extent. The percentage of absorption during the first month was relatively rapid for all four groups. The rate of absorption progressively decreased with each succeeding month, the curve tending to level after the hundredth day. The decrease in rate of absorption was inversely proportional to the absolute weight of the pellet.

4. The average daily absorption in milligrams in the case of pellets of 100 mg. for example, is at first about 1 mg. per day and then falls off gradually, reaching about 0.5 mg. by the 100th day, and about 0.35 mg. by the 170th day. Since the daily absorption follows a more or less constant curve for pellets of certain weight it should be possible to calculate the effective life of a pellet of a given weight.

5. The rate of absorption is mainly a physical phenomenon depending on the surface area exposed to the dissolving action of tissue fluids. Influencing factors are the density of the pellet, the size of the particles (crystals) that comprise the pellet, the surface area and the site of implantation.

#### ADDENDUM

Since the submission of this paper a 200-mg. pellet removed 112 days after implantation, showed 41.5 per cent absorption (83 mg.). If this value were plotted on fig. 3 it would fall on curve A, the absorption curve for 200-mg. pellets.

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# 17-Ketosteroid Excretion and Seminal Function<sup>1</sup>

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A PREVIOUS REPORT by members of our group dealt with the correlation of seminal findings and basal metabolic rates in men investigated because of presumed sterility (1). A number of individuals, including some of those previously reported and others since that time, has been investigated with regard to 17-ketosteroid levels and seminal biometric data. The present communication reports these studies.

## METHODS

A group of 57 males was investigated. All patients underwent medical, urologic and endocrine surveys. All had determinations of basal metabolic rates and roentgenograms of the sella turcica made. Roentgenologic studies of bone age were made when these appeared to be indicated. No therapy was given prior to these studies.

The majority of seminal specimens was secured by masturbation after 5 to 7 days of continence. As a rule, studies were initiated within 7 to 12 minutes after the specimen was obtained.

The method for seminal evaluation was essentially that of Meaker (2). This has been described in detail by one of us (3). The accepted criteria for normal seminal values were as follows: *volume*, 3 to 4 cc.; *abnormal morphology*, 20 per cent or less; *spermatozoal motility*, 80 per cent or more; *number of spermatozoa per cc.*, 60,000,000 as the lower limit; *number of spermatozoa for the entire ejaculate*, 240,000,000 as the lower limit. The seminal findings reported are those obtained during the times when 17-ketosteroid studies were being made.

Determinations of 17-ketosteroids were made on 4 to 7 consecutive 24-hour specimens of urine of each

patient by the colorimetric method of Oesting (4, 5) after extraction of the urine by the method of two of us (6). The 17-ketosteroid values used in reporting our data represent the averages of daily determinations, expressed as international units of androsterone. These findings have not been correlated with bio-assays, hence no assessment of the androgenicity of the urines of these patients can be made.

## DATA

The ages of the 57 patients studied ranged from 15 to 49 years. Table 1 correlates 5-year age epochs with the seminal values and with the 17-ketosteroid levels of 50 of the 57 patients. Seven patients with presumed androgenic deficiency were not included in this table.

The patients studied have been grouped as follows: a), those with essentially normal seminal values; b), those with presumed androgenic deficiency; c), those with decreased seminal values.

Data on 11 patients with essentially normal seminal values comprise the first group. Table 2 correlates the seminal values and 17-ketosteroid levels of these 11 patients.

Data on 7 patients who had androgenic deficiencies are presented in table 3.

Data on 39 patients with decreased seminal values are presented in tables 4 to 8 inclusive.

## DISCUSSION

From the data presented, a correlation apparently exists between the age groups and the 17-ketosteroid levels. A peak in the excretion values is reached gradually between the ages of 35 and 40 years. There is a rather marked decline in values by the end of the 45th to 49th years. This trend may reflect a qualitative change in urinary 17-ketosteroids with regard to active and inactive members of the group, and may be indicative of a stabilization of the gonado-adrenopituitary system which has been envisioned by some

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workers as being a phase in the sexual aging of the male. There is apparently no correlation between the age of the patients studied and their seminal values.

An analysis of the data permits the establishment of no clear-cut relationship between values in the patients having higher 17-ketosteroid levels and the patients having accepted standards for normalcy, as regards seminal values. It is true that the 11 patients who had essentially normal seminal values had, as

TABLE 1 CORRELATION OF AGES IN 5-YEAR EPOCHS WITH SEMINAL VALUES AND 17-KETOSTEROID LEVELS

| 5 Year Age Epochs | cc | %   | %  | 17 Ketosteroids | 1 U         | 1 U |
|-------------------|----|-----|----|-----------------|-------------|-----|
| 15-19             | 1  | 0.5 | 27 | 70              | 187,000,000 | 24  |
| 20-24             | 6  | 3.8 | 27 | 66              | 123,000,000 | 70  |
| 25-29             | 14 | 3.9 | 33 | 62              | 61,000,000  | 83  |
| 30-34             | 13 | 4.3 | 39 | 66              | 121,000,000 | 98  |
| 35-39             | 8  | 3.8 | 36 | 55              | 105,000,000 | 116 |
| 40-44             | 4  | 2.8 | 33 | 50              | 93,000,000  | 64  |
| 45-49             | 4  | 3.1 | 29 | 71              | 190,300,000 | 61  |

TABLE 2 CORRELATION OF ESSENTIALLY NORMAL SEMINAL VALUES WITH 17-KETOSTEROID LEVELS, LISTED IN ORDER OF DECREASING 17-KETOSTEROID VALUES

| Patient       | Age   | Volume | Abnormal morphology | Motility | Spermatozoa per cc | Average Daily 17 Ketosteroid |
|---------------|-------|--------|---------------------|----------|--------------------|------------------------------|
| 1             | years | cc     | %                   | %        | %                  | 1 U                          |
| 2             | 37    | 3.0    | 19                  | 75       | 81,000,000         | 212                          |
| 3             | 37    | 3.0    | 20                  | 79       | 166,000,000        | 203                          |
| 4             | 30    | 3.0    | 20                  | 91       | 255,000,000        | 182                          |
| 5             | 36    | 3.0    | 25                  | 85       | 101,000,000        | 169                          |
| 6             | 28    | 4.0    | 23                  | 80       | 125,000,000        | 131                          |
| Average       | 31.2  | 3.4    | 21                  | 81       | 138,000,000        | 179                          |
| 7             | 34    | 5.0    | 14                  | 95       | 161,000,000        | 105                          |
| 8             | 26    | 5.0    | 14                  | 75       | 70,000,000         | 86                           |
| 9             | 32    | 4.1    | 22                  | 80       | 90,000,000         | 66                           |
| 10            | 30    | 3.5    | 20                  | 60       | 213,000,000        | 58                           |
| 11            | 31    | 5.1    | 30                  | 95       | 218,000,000        | 49                           |
| 12            | 48    | 2.5    | 18                  | 90       | 117,500,000        | 21                           |
| Average       | 32.1  | 4.0    | 18                  | 88       | 161,710,000        | 63                           |
| Grand Average | 31.8  | 3.9    | 19                  | 84       | 151,000,000        | 115                          |

TABLE 3 CORRELATION OF SEMINAL VALUES AND 17-KETOSTEROID LEVELS OF PATIENTS WITH PRESUMED ANDROGENIC DEFICIENCY

| Patient | Age   | Significant Symptoms and Findings | Volume | Abnormal morphology | Motility | Spermatozoa per cc              | Average Daily 17 Ketosteroid |
|---------|-------|-----------------------------------|--------|---------------------|----------|---------------------------------|------------------------------|
| 1       | years |                                   | cc     | %                   | %        | %                               | 1 U                          |
| 2       | 42    | Testicular atrophy, bilateral     | 0.5    | 100                 | 0        | No spermatozoa seen             | 59                           |
| 3       | 42    | Testicular atrophy, bilateral     | 1.0    | 20                  | 70       | Total of 4 observed 100,000,000 | 26                           |
| 4       | 22    | Adolescent testicular failure     | 0.1    | 0                   | 0        | No spermatozoa seen             | 18                           |
| 5       | 28    | Cryptorchidism, bilateral         | 0.9    | 76                  | 30       | 6,000,000                       | 62                           |
| 6       | 30    | Decreased seminal values          | 7.5    | 75                  | 51       | 233,000                         | 116                          |
| 7       | 46    | Mild climacteric                  | 6.0    | 73                  | 15       | 262,000                         | 86                           |
| Average | 34.1  |                                   | 3.9    | 49                  | 22       | 15,230,000                      | 61                           |

TABLE 4 CORRELATION OF 10 HIGHEST 17-KETOSTEROID LEVELS WITH CORRESPONDING SEMINAL VALUES

| Patient | Age   | Volume | Abnormal morphology | Motility | Spermatozoa per cc | Average Daily 17 Ketosteroids |
|---------|-------|--------|---------------------|----------|--------------------|-------------------------------|
| 1       | years | cc     | %                   | %        | %                  | 1 U                           |
| 2       | 24    | 2.0    | 21                  | 80       | 91,000,000         | 147                           |
| 3       | 33    | 6.0    | 31                  | 90       | 245,000,000        | 147                           |
| 4       | 40    | 4.5    | 25                  | 59       | 177,500,000        | 145                           |
| 5       | 31    | 3.5    | 50                  | 30       | 40,000,000         | 144                           |
| 6       | 38    | 7.0    | 28                  | 65       | 92,500,000         | 143                           |
| 7       | 38    | 3.5    | 41                  | 90       | 160,000,000        | 135                           |
| 8       | 33    | 1.0    | 24                  | 70       | 95,000,000         | 132                           |
| 9       | 21    | 4.5    | 21                  | 60       | 110,000,000        | 125                           |
| 10      | 32    | 2.0    | 43                  | 5        | 40,000,000         | 101                           |
| 11      | 37    | 1.5    | 18                  | 55       | 160,000,000        | 100                           |
| Average | 32.7  | 4.0    | 31                  | 59       | 121,500,000        | 134                           |

TABLE 5 CORRELATION OF 10 LOWEST 17-KETOSTEROID LEVELS WITH CORRESPONDING SEMINAL VALUES

| Patient | Age   | Volume | Abnormal morphology | Motility | Spermatozoa per cc | Average Daily 17 Ketosteroids |
|---------|-------|--------|---------------------|----------|--------------------|-------------------------------|
| 1       | years | cc     | %                   | %        | %                  | 1 U                           |
| 2       | 49    | 2.0    | 76                  | 3        | 250,000            | 10                            |
| 3       | 23    | 1.5    | 16                  | 60       | 67,000,000         | 16                            |
| 4       | 21    | 1.0    | 83                  | 1        | 2,700,000          | 18                            |
| 5       | 15    | 0.5    | 27                  | 70       | 155,000,000        | 24                            |
| 6       | 45    | 2.5    | 41                  | 23       | 2,165,500          | 27                            |
| 7       | 37    | 4.0    | 11                  | 15       | 56,000,000         | 34                            |
| 8       | 24    | 7.0    | 30                  | 65       | 32,000,000         | 42                            |
| 9       | 42    | 1.0    | 41                  | 70       | 170,000,000        | 44                            |
| 10      | 49    | 1.5    | 27                  | 60       | 80,000,000         | 50                            |
| 11      | 49    | 1.5    | 36                  | 90       | 135,000,000        | 50                            |
| Average | 32.2  | 2.8    | 43                  | 47       | 75,851,000         | 32                            |

TABLE 6 CORRELATION OF DATA ON PATIENTS OF GROUP WITH GREATEST NUMBER OF SPERMATOZOA PER CUBIC CENTIMETER OF SEMINAL FLUID

| Patient | Age   | Volume | Abnormal morphology | Motility | Spermatozoa per cc | Average Daily 17 Ketosteroids |
|---------|-------|--------|---------------------|----------|--------------------|-------------------------------|
| 1       | years | cc     | %                   | %        | %                  | 1 U                           |
| 2       | 48    | 4.00   | 30                  | 80       | 335,000,000        | 57                            |
| 3       | 40    | 3.00   | 27                  | 90       | 267,500,000        | 60                            |
| 4       | 33    | 6.00   | 31                  | 90       | 245,000,000        | 147                           |
| 5       | 35    | 6.25   | 25                  | 63       | 232,500,000        | 145                           |
| 6       | 40    | 4.50   | 25                  | 50       | 177,500,000        | 141                           |
| 7       | 30    | 5.00   | 12                  | 60       | 112,500,000        | 59                            |
| 8       | 31    | 5.00   | 18                  | 10       | 110,500,000        | 83                            |
| 9       | 31    | 3.50   | 33                  | 48       | 120,000,000        | 73                            |
| 10      | 27    | 6.00   | 33                  | 80       | 110,000,000        | 140                           |
| 11      | 38    | 7.00   | 28                  | 61       | 92,500,000         | 80                            |
| Average | 37.7  | 5.2    | 26                  | 68       | 185,200,000        | 90                            |

a group, the highest 17-ketosteroid levels. However, when the data on these patients are subdivided (table 2) into two groups, one which has levels higher, and one which has levels lower, than the mean figure of 115 U, then the group having the lower 17-ketosteroid levels averages higher seminal values in every respect. The mean 17-ketosteroid level for the 50 patients, not including those with presumed androgenic deficiency, is 86 U. If the data on these patients are divided into two groups, a), those patients with 17-ketosteroid levels of 86 U or higher and b), those patients with 17-ketosteroid levels less than 86 U, no significant correlations appear, although the group levels are 139 U and 56 U, respectively.



TABLE 7. CORRELATION OF DATA ON PATIENTS OF GROUP WITH SMALLEST NUMBER OF SPERMATOZOA PER CUBIC CENTIMETER OF SEMINAL FLUID

| Patient | Age   | Seminal Values |                     |          |   | Average Daily 17-Keto-steroids |
|---------|-------|----------------|---------------------|----------|---|--------------------------------|
|         |       | Volume         | Abnormal morphology | Motility | Spermatozoa per cc                          |                                |
|         | years | cc             | %                   | %        |   | I U                            |
| 1       | 32    | 2 0            | 43                  | 5        | 40,000,000                                  | 101                            |
| 2       | 34    | 4 5            | 29                  | 58       | 37,500,000                                  | 70                             |
| 3       | 28    | 1 5            | 50                  | 30       | 13,500,000                                  | 76                             |
| 4       | 29    | 0 1            | 45                  | 40       | 10,500,000                                  | 62                             |
| 5       | 28    | 6 0            | 60                  | 85       | 5,000,000                                   | 74                             |
| 6       | 25    | 1 0            | 83                  | 1        | 2,700,000                                   | 18                             |
| 7       | 45    | 2 5            | 41                  | 23       | 2,162,500                                   | 27                             |
| 8       | 40    | 2 0            | 76                  | 2        | 250,000                                     | 10                             |
| 9       | 37    | 1 75           | 100                 | 20       | Total of 12 observed<br>1 Spermatozoon seen | 88                             |
| 10      | 28    | 0 75           |                     |          |   | 94                             |
| Average | 32 6  | 2 6            | 43                  | 26       | 11,161,000                                  | 62                             |

The lack of correlation between data on patients with higher 17-ketosteroid levels and those patients with normal seminal values is reflected also in tables 4 and 6.

There exists a general relationship between low 17-ketosteroid levels and decreased seminal values. The data in tables 3, 5 and 7 supply this evidence. This is not an unexpected finding. It is believed generally that urinary 17-ketosteroids originate in the adrenal cortex. Urinary extracts of these substances include both the unmodified compounds and those changed by testicular metabolism. Seventeen-ketosteroid determinations, then, may be indicative indirectly of the androgenic or metabolized products present. This is based upon observations that active and inactive members of the non-phenolic 17-ketosteroid group are present in urine of normal individuals in the ratio of approximately 1:1 (7-9). Hence, the patients who had decreased seminal values and low 17-ketosteroid levels probably had some degree of androgenic deficiency which was reflected in the seminal values. It has been a common working premise with us that seminal values, as a rule, afford a good index of androgenic activity, except in those patients in whom intrinsic damage or insufficiency of the seminal epithelium exists.

Some of these patients had 17-ketosteroid levels of the same low order as those associated with hypofunction of the adrenal cortex (7, 8). However, none

TABLE 8. SEMINAL VALUES AND 17-KETOSTEROID LEVELS OF 6 PATIENTS NOT INCLUDED IN FOUR PRECEDING TABLES

| Patient | Age   | Seminal Values |                     |          |                    | Average Daily 17 Keto steroids |
|---------|-------|----------------|---------------------|----------|--------------------|--------------------------------|
|         |       | Volume         | Abnormal morphology | Motility | Spermatozoa per cc |                                |
|         | years | cc             | %                   | %        |                    | I U                            |
| 1       | 29    | 6 5            | 34                  | 70       | 90,000,000         | 85                             |
| 2       | 32    | 3 0            | 40                  | 90       | 79,500,000         | 85                             |
| 3       | 23    | 4 0            | 16                  | 60       | 67,500,000         | 16                             |
| 4       | 25    | 5 5            | 26                  | 80       | 49,000,000         | 54                             |
| 5       | 21    | 8 5            | 40                  | 38       | 45,000,000         | 62                             |
| 6       | 29    | 4 75           | 35                  | 50       | 42,500,000         | 79                             |
| Average | 26 5  | 5 4            | 32                  | 64       | 62,100,000         | 64                             |

of them presented signs or symptoms of any adrenal disease.

When the variously encountered biometric abnormalities of the spermatozoa of patients were arranged according to ages of these patients and their 17-ketosteroid levels, no significant correlations were apparent. Likewise, no correlation existed between the 17-ketosteroid levels of patients, the degree of viscosity and of turbidity of their seminal fluids, and the viability of their spermatozoa.

SUMMARY

Studies of 17-ketosteroid levels and of seminal values were made on 57 males, aged 15 to 49 years. Significant correlation apparently existed between the age of patients and the 17-ketosteroid excretion, and between the occurrence of decreased 17-ketosteroid levels and deficient seminal values. No correlation between the age of the patients and the seminal values, or between the occurrence of high 17-ketosteroid levels and normal seminal values were apparent.

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# Syndrome of Nocturnal Frequency Alleviated by Testosterone Propionate<sup>1</sup>

## [Androgens and Nocturia]

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IN WOMEN, disturbances of micturition may occur without evidence of cardio vascular-renal disease, anatomic defects in the urinary tract or genito urinary infection. It is admitted that psychogenic factors frequently play an important rôle in functional bladder disorders, but what has not been readily appreciated is that nocturia, urgency, and incontinence may have a hormonal basis. We wish to draw attention to a syndrome of nocturnal frequency in women who may or may not have disturbances of micturition during the day. The routine urinary findings are usually negative or of little significance. Stigmata of endocrine imbalance such as menorrhagia, dysmenorrhea, fibromyomata may be present in the premenopausal group and vasomotor disturbances or atrophic vaginitis in the menopausal group.

In March, 1941, we reported (1) before the Southeastern Surgical Congress on the palliative therapy of fibromyomata uteri by administration of chemically pure androgenic substances. Attention was brought at that time to a pertinent observation, to wit, that moderate to severe nocturia was a universal complaint of patients with massive uterine fibroids and that amelioration of this syndrome followed the subfascial implantation of pellets of testosterone propionate. The idea has gained currency that nocturia associated with fibromyomata was due to pressure on the bladder. Although this fact has been perpetuated both in textbooks and in teaching, it may well be fallacious, as subsequent facts tend to demonstrate. Frequently, in spite of but minor reduction in size of massive fibromyomata following implantation of testosterone propionate pellets, the nocturia was alleviated

years had pellets of testosterone propionate<sup>2</sup> implanted subfascially for the treatment of various gynecic disorders. From 1 to 4 pellets were implanted at one time. The pellets varied in weight from 22 to 200 mg. Although the average dosage was about 100 mg, nevertheless as little as 25 and as much as 400 mg was employed. These patients, except for a few recent cases, have been under observation for 6 to 21 months. Careful evaluation of complaints yielded the information that 28 of the 63 women were regularly disturbed by urgency after retiring. Only those who, with regularity, had to void two or more times per night were included in this series. Nocturia varied from 2 to 10 times per night in different individuals but as a rule the disturbance was more or less constant for the same person. Associated with nocturia there was, not infrequently, diurnal frequency and dysuria. Of the 28 patients in question, 3 were menopausal cases and 19 had fibromyomata uteri with or without menstrual irregularities. In every one of the 28 patients the nocturnal frequency was wholly or for the greater part alleviated after pellet implantation. In several, the symptoms partially or wholly recurred with complete absorption of the pellets. It might be added, however, that of the remaining 35 patients in this series without urinary disturbances, nocturia developed in three following pellet implantation.

**Electrolyte metabolism.** In an effort to learn the reason for the alleviation of the nocturnal frequency, repeated blood chemistry determinations were performed on many of the patients to detect possible changes in electrolyte metabolism. Blood sodium, potassium, calcium, along with sugar, NPN, uric acid and creatinine determinations were made. The values obtained were within the limits of normal.

### OBSERVATIONS

Sixty-three women ranging in age from 25 to 58

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<sup>2</sup> The pellets were made by

were  
New  
Dr R

*Water balance.* Water intake and output before and after pellet implantation was measured in but few patients. This procedure did not prove to be practical because of the need for long hospitalization. Many patients volunteered the information that they drank water much more freely before pellet implantation and that the desire for water was much lessened after this procedure. It may be, then, that alleviation of nocturnal frequency may be due not to water retention but to the effect of the steroid on pituitary activity in correcting a subclinical or mild diabetes insipidus.

*Cystometric studies.* Occasional cystometric studies were done. One patient who complained chiefly of nocturia, had cystometric studies before and after pellet implantation. Coincident with the clinical improvement, the cystometric studies revealed greater bladder capacity as well as greater tolerance of bladder pressure.

#### CASE REPORTS

*L. L.*, aged 35, an obese colored female, complained of marked nocturia. Although she was disturbed every 15 to 30 minutes during the night, she had no disturbances of micturition during the day. She drank water rather freely. Routine urine analysis revealed nothing unusual. Cystometric studies revealed that she could tolerate a bladder pressure of 22 mm. of mercury and a maximum capacity of 400 cc. of water. Pelvic examination revealed a fibromyoma of the uterus which extended above the level of the umbilicus. Her menstrual periods were regular, of 4 days' duration with moderate pain on the first day. On Oct. 18, 1941, a pellet of 104 mg. of testosterone propionate was implanted subfascially. There was an immediate amelioration of the urinary symptoms and only occasionally was she disturbed so much as once per night. Two months after pellet implantation she volunteered the information that her fluid intake was now greatly reduced because of a slackening of her desire for water. Later on there was a gradual return to increased fluid intake but without any recurrence of nocturia. The menstrual cycle was in no way disturbed and the dysmenorrhea was but slightly alleviated. On April 9, 1942, she was submitted to laparotomy. The fibromyoma had decreased somewhat in size, for just previous to operation the tumor could be palpated one inch below the level of the umbilicus. During the 6-month period that she was under observation the blood pressure remained constant. Her weight increased from 231 to 243 lb. Libido began to increase considerably about 5 weeks after pellet implantation and began to subside just before operation. No evidence of virilization occurred. The pellet was recovered at the time of laparotomy and 80 mg. was absorbed over a period of 177 days. Cystometric studies just prior to operation revealed an improvement in bladder capacity which was up to 650 cc. and a tolerance of bladder pressure of 50 mm. of mercury. The remarkable improvement in the nocturnal frequency which persisted throughout the period of observation must be attributed to the testosterone propionate.

*A. J.*, a colored female, age 36, complained of a mass in her abdomen, hypermenorrhea, severe dysmenorrhea, and a nocturia of 10 to 20 times per night. Examination revealed a large fibromyoma extending 4 cm. above the umbilicus. Two pellets totalling 150 mg. of testosterone propionate were implanted subfascially on July 28, 1941. The menstrual periods that followed were regular, painless and the flow was reduced to 4 to 5 days. The nocturia which had been present for 5 years completely subsided within 2 weeks after pellet implantation. Libido which had been good before pellet implantation became very good and her sense of well being improved. The blood pressure remained more or less constant and there was a weight increase from 183 to 195 lb. There was no evidence of virilization during the 8 months she was under observation. Routine urine analyses were negative and blood chemistry determinations were within the limits of normal. About 6 months after pellet implantation there was a moderate recurrence of the excessive bleeding and the dysmenorrhea but the symptoms of polyuria and nocturia remained in complete abeyance. On March 13, 1942, a total hysterectomy was done. The pathologist reported multiple interstitial and subserous fibromyoma up to 11 cm. in diameter. The remarkable alleviation of the nocturnal frequency in this patient must be attributed to the testosterone propionate.

*M. L. P.*, a white female 28 years old, complained of hypermenorrhea, severe dysmenorrhea, nocturia of 6 to 10 times per night and frequency during the day of 5 to 6 times. The bladder disorder had been more or less persistent for the past 5 years. She had a desire to drink quantities of water. Prior and subsequent to implantation of two 200-mg. pellets of testosterone propionate fluid intake and output studies were done. Soon after the implantation, nocturia decreased to once per night and soon thereafter to only once in every few nights. The frequency during the day was alleviated. Thus far, the menstrual cycle has remained regular, the flow normal and painless. Libido, which had been negligible prior to pellet implantation improved so remarkably that she again fell in love with her husband. She claimed that she felt more maternal and her sense of well being had improved. No evidence of virilization developed during the period of observation. The patient still drinks lots of water but not as much as before pellet implantation. Her weight has increased from 138 to 140 lb. Urine analyses before and after implantation were negative and blood chemistry studies (sugar, NPN, uric acid, creatinine, Na, K, Ca) repeated at weekly intervals have remained within the range of normal. The complete alleviation of the urinary symptoms must be attributed to the effect of testosterone propionate.

#### DISCUSSION

In the experimental animal (rat) high dosages of estrogen cause water retention (2). Such antidiuretic effect is characteristic not only of estrogens but also of other physiologically active steroid hormones such as androgens and progesterone (3). In the human being it may well be that estrogens and testosterone are antidiuretic and this may account for the alleviation of frequency and nocturia. However, we have

not been convinced that progesterone has similar properties. In fact, in patients in whom pellets of progesterone have been implanted (150-300 mg.) no consistent results, insofar as an increase or decrease of the symptoms of frequency and nocturia have been observed. (4) Selye believes that in the experimental animal (rat) progesterone and desoxycorticosterone are diuretic and thus differ in their action from that of testosterone. In human beings crystalline testosterone propionate pellets implanted subfascially proved diuretic in only 3 of the 35 patients who did not have disorders of micturition and was antidiuretic in all of the 28 patients who did have nocturia, with or without diurnal distress. We also found that moderately large doses of testosterone propionate (25 mg.) administered parenterally at 4 to 7 day intervals were successful in diminishing the severity of urinary distress in several menopausal patients. Mocquot and Moricard (5) were the first to note that functional disorders of micturition in menopausal women could be ameliorated by testosterone. Small doses of testosterone propionate (5 to 10 mg.) have been used in the alleviation of premenstrual edema when associated with premenstrual tension. (6) Small doses of progesterone may likewise be used. It appears that small doses of these steroids may have mild diuretic properties, although this point has not been substantiated. Recently a young surgically castrate female of 26 years of age complained of vasomotor disturbances, dysuria, urgency and marked nocturnal frequency. She had an intractable trichomonas vaginalis which had been incriminated as responsible for the genito urinary complaints. Thirty mg. of estradiol<sup>2</sup> and 150 mg. of progesterone<sup>3</sup> were implanted subfascially. The vasomotor flushes were gradually alleviated, the relief of the urinary symptoms, however, was immediate and dramatic in spite of the persistence of the trichomonas vaginalis. A few months later spontaneous extrusion of the pellets occurred with subsequent recurrence of the urinary disturbance.

There are many indications that the genito urinary tract is probably under hormonal influence. This may be adduced from the following facts: a), In pregnancy, hypertrophy of the ureters, hydronephrosis and other genito urinary disturbances readily occur; b), In the climacteric, urinary symptoms attributable to an estrogen deficit such as urinary frequency, urgency and incontinence, are common accompaniments of the menopausal syndrome. These symptoms, according to Simon et al. (7), are usually refractory to orthodox treatment and all but few patients may

be kept symptom-free on a maintenance dose of estrogens. c), Certain components of the genito urinary system are under hormonal influence. Korenchevsky and his colleagues (8) have long known that androgens were nephrotrophic causing increase in weight of kidneys and in size of tubules in both normal and castrate female rats.

It has been observed in the mouse, that males always have considerably larger kidneys than females of the same size. Castration in males reduces the size of the kidney to the female level, while ovariectomy exerts no significant effect on the female kidney. Selye (9) has shown that testosterone does not merely increase the size of the kidney of the mouse but actually protects the tubular cells against the damaging effect of sublimate. This protective action of testosterone is evident in both sexes but is somewhat more marked in female than in male mice. Furthermore, Selye and Fridman (10) have shown by experiments on the mouse that renal atrophy which usually develops subsequent to the hydronephrosis caused by ligation of the ureter may be inhibited and delayed by testosterone administration. Selye (11) believes that testosterone exerts a specific action on kidney tissue and histologically such kidneys are characterized by pronounced hypertrophy of the epithelium of the proximal and distal convoluted tubules and of the epithelium lining the parietal lamina of Bowman's capsules. Albert (12), working in Selye's laboratory, has recently shown that in the rat the enlargement of the pituitary and adrenals caused by estradiol could be inhibited by testosterone, the renotrophic action of testosterone, however, could not be prevented by simultaneous injections of estradiol.

#### CONCLUSIONS

1 Among the frequent causes of nocturia there may be listed cardiovascular-renal disease, anatomic defects in the urinary tract, genito urinary infections and psychogenic factors. A common causative factor heretofore not readily appreciated is the hormonal basis for nocturnal frequency.

2 In a series of 63 women in whom 1 to 4 pellets of testosterone propionate were implanted subfascially for various gynecic disorders, it was noted that 28 of them suffered from nocturnal frequency. Although 19 of the 28 women with this syndrome had fibromyomata uteri, the nocturia nevertheless was wholly or partially alleviated in all of them following the implantation. For this reason it is felt that the belief perpetuated in textbooks and teaching may well be fallacious—that nocturia associated with fibromyomata is due to pressure on the bladder.

3 Nocturia and diurnal distress for which no pathologic basis can be ascertained often prove refrac-

<sup>2</sup> Estradiol and progesterone pellets were supplied through the courtesy of Dr. W. H. Stoner of the Schering Corporation, Bloomfield, New Jersey.

tive to orthodox methods of treatment. Before contemplating surgery for the relief of this syndrome it is well to reconsider the rôle played by such factors as fibromyomata or a markedly anteverted mobile uterus pressing unduly on the bladder or certain anatomic defects of the bladder such as mild cystocele or urethrocele. The frequency of bladder discomfort incident to these factors has been overstressed. The common tendency to operate upon such cases appears unwarranted before an ample course of estrogens or androgens has first been tried.

4. Evidence has accumulated that the physiologic processes of the genito-urinary tract may be influenced by various hormones. Androgens are nephrotrophic. Testosterone exerts a specific action on kidney tissue. The reasons for the amelioration of certain disorders of micturition following steroid therapy may be a direct sequence to hormonal action either on kidney function, bladder tone, pituitary activity, water balance, electrolyte metabolism or some other mechanism at present not understood.

5. As a result of our experience, we may say that sterile crystalline testosterone propionate pellets implanted subfascially will ameliorate the syndrome of nocturnal frequency herein described. From 25 to 400 mg. may well be used without fear of arrhenimetic phenomena.

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# Testosterone Propionate in the Treatment of Angina Pectoris

[Angina Pectoris]

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EXTENSIVE EXPERIMENTATION in animals has demonstrated that the sex hormones very definitely effect certain non sex organs of their bodies. Ratschow and Kosterman (1), using androgens experimentally in rats, report an absence of sloughing following severe vasoconstriction by ergotamine. Korenchevsky (2) and his coworkers report changes in weight and in histologic structure in rat livers and hearts following administration of androsterone or testosterone esters to the animals, attributing certain hepatotropic and cardiotropic properties to these hormones. That these hormones also exert nephrotrophic effects was reported in an earlier paper by the same authors. Therapeutic applicability of these properties suggests itself in disorders of these organs in human beings and it is the purpose of this report to describe the results of such treatment in suitable cases of angina pectoris and of angina of effort.<sup>1</sup>

The effect of testosterone on the human cardiovascular system has been the subject of but few reports in the literature thus far. Walker (3) reported symptomatic improvement in peripheral circulation following testosterone administration in 6 cases, and Edwards, Hamilton, and Duntley (4) report an increase in arterialization after treatment with testosterone propionate in 7 male patients, 3 suffering from thromboangitis obliterans and 4 from arteriosclerosis. Studying the effects of testosterone on metabolism, Jones, McCullagh, McCullagh, and Buckaloo (5) report an increased basal metabolic rate in 11 patients studied and, moreover, an increase or decrease in velocity of blood flow paralleling rise or fall in basal metabolic rate as influenced by testosterone. Reports thus far are conflicting with regard to the effect of testosterone on blood pressure although there are indications that certain cases of hypertension may be favorably influenced (6). Among clinical studies of the effectiveness of the hormones in cases of angina pectoris *per se* is that reported by Lesser (7). This

investigator administered testosterone propionate to 24 patients with angina pectoris in order to determine its influence on the frequency and/or severity of attacks. Depending upon severity of symptoms and response to treatment, the dosage schedule employed was 25 mg every 2 to 5 days for a total of 5 to 25 injections. All patients improved as measured by diminution in frequency, duration, and severity of their anginal attacks and by their ability to increase physical activity without precipitating attacks. This improvement persisted for 2 to 12 months following interruption of therapy. Similar results did not follow injections of sterile sesame oil given as a control measure.

## CASE REPORTS

All cases herein reported presented a typical history and a clinical picture of angina pectoris or of sub-sternal pain on effort. Most of these patients carried nitroglycerine to relieve attacks. The basal metabolic rate was abnormally low in each. Prior to treatment with testosterone propionate, one patient had been unable to walk a distance of one half of a city block after lunch for the past 5 years without precipitating an attack. In 3 cases the blood pressure was 150 mm Hg systolic or more, in all 3 cases it came down to 130 mm Hg or less following the administration of testosterone propionate. The general appearance of the skin changed from a sallow to a more natural pinkish tone and all of the patients expressed a feeling of euphoria. Three had headaches in the late afternoon which disappeared after the second and third injection. An increased endurance, mental agility and ambition was apparent to the patients as well as to their friends. Not one has had a return of angina or even distress since treatment began.

**PH Age 75** For 5 years he had been experiencing difficulty in breathing while walking and suffered sharp pains in the precordial region concomitantly. Nitroglycerine tablets relieved the pain. He was unable to walk half a block after lunch without an attack. His B M R was minus 18, pulse 60 at rest, temperature 97.6° F, blood pressure 100 over 70 mm Hg. Thyroid medication seemed to increase the pain. Starting in February, 1941, he was

<sup>1</sup>Received for publication March 24, 1942.

<sup>2</sup>The testosterone propionate (Neo Hombreol) used in this study was supplied by Roche-Organon, Inc., Nutley, N. J., through courtesy of M. C. James, M.D.

given 25 mg. of testosterone propionate 3 times a week, continuing for 2 months. After the second injection he was able to walk 3 blocks without any discomfort. The number of injections was decreased to 2 a week and later to 1; for the past 3 months one 25 mg. injection per month has sufficed. His color, which was of a grayish hue, is now a healthy pink. Blood pressure is now 120 over 80 mm. Hg, pulse 72 at rest, temperature 98° F. He walks 4 or 5 blocks a day without discomfort and states that his mental and physical endurance have increased to a marked extent.

**W.C. Age 54.** For 6 years he has had substernal pain on effort, definitely diagnosed in his case as a manifestation of coronary artery disease. His color was sallow and he appeared very much older than his years. Blood pressure was 160 over 94 mm. Hg, pulse 62 at rest, temperature 98° F. B.M.R. was minus 15. He had been taking 5 grains of thyroid a day. He was very tired and lacked energy to complete his usual day's work. Treatment was started with 25 mg. of testosterone propionate 3 times a week; thyroid medication was stopped at this point. During the second week he was able to walk 5 blocks during a very cold day without precordial discomfort. He had more energy and could work a full day without tiring. After one month his color improved and he appeared much younger than when he started to take the injections. During the past 3 months he has been taking one injection of 25 mg. a month and has had no return of anginal symptoms. His endurance has increased and he is able to climb two flights of stairs with ease.

**E.D.L. Age 52.** Has had angina pectoris for the past 7 years, the attacks being precipitated by effort. The electrocardiogram, as in the other cases, revealed no myocardial change. In addition to the anginal syndrome he had severe headaches in the late afternoon, and was ready for bed at 8 o'clock every night. Twenty-five mg. of testosterone propionate was given 3 times a week for 1 month. Headache was relieved after the second injection and anginal symptoms disappeared after the fourth. The frequency of injections was gradually reduced to 1 a month. He is less fatigued after physical and mental effort and able to climb 3 flights of stairs without discomfort.

**C.D. Age 60.** Has had anginal symptoms for the past 3 years and has been unable to walk more than a block without substernal pain. Nitroglycerine tablets relieved pain. The pulse was 70, blood pressure 110 over 70 mm. Hg. Twenty-five mg. of testosterone propionate was given 3 times a week for 1 month. After the third injection anginal symptoms disappeared, and he was able to walk several blocks without distress. At the end of 3 weeks his pulse was 72, blood pressure 120 over 80 mm. Hg. There has been a decided improvement in mental and physical endurance and he has been free of substernal pain for 11 months.

**M.A.P. Age 67.** For more than a year he had experienced pain in his chest on walking up a slight hill on his way home. Angina pectoris was diagnosed and nitroglycerine prescribed. Physical examination was negative except for a blood pressure of 160 over 92 mm. Hg. He

would have 5 or 6 attacks during the day and even walking on level ground for more than one block would bring on precordial distress. He was given 25 mg. of testosterone propionate 3 times a week for 6 weeks. After the sixth injection he said he had no discomfort on walking up the hill to his home. Treatment was continued for several months longer, employing the same dosage schedule, but it was later decreased to two injections a month and later to one. He is now able to walk up two flights of stairs and several city blocks without return of anginal symptoms. His blood pressure is now 140 over 82 mm. Hg.

**C.T.E. Age 61.** Has had angina pectoris for 3 years and always carried nitroglycerine tablets for relief of pain. He was unable to go up stairs without an attack and would have 3 and 4 'spells' a day. Physical examination showed a man older than his years, blood pressure 100 over 70 mm. Hg, pulse 65, temperature 98° F. Testosterone propionate was given in 25 mg. doses 3 times a week for 3 weeks. It was then reduced to twice a week and later to once a month. After the sixth injection he had no further anginal symptoms and could walk up two flights of stairs or four blocks, even in cold weather without a return of precordial distress. He has now been free from pain on effort for 6 months. Blood pressure is 116 over 74 mm. Hg, pulse 70.

**H.C.E. Age 66.** Complained of pain in substernal region on effort and was unable to walk two blocks or climb one flight of stairs without discomfort. He complained, also, of cold hands and feet and lack of energy. Twenty-five mg. of testosterone propionate was given 3 times a week for 6 weeks. After the sixth injection he was able to climb three flights of stairs and walk five blocks without precordial discomfort. Treatment was reduced to one injection a month and 5 mg. of methyl testosterone orally a day. No anginal symptoms have been present for the past 11 months.

#### COMMENT

Upon analyzing these case reports it will be seen that 7 patients ranging in age from 52 to 75 years who presented the clinical syndrome of angina pectoris or substernal pain on effort, were treated with testosterone propionate; 25 mg. of this substance was injected intramuscularly 3 times a week for 6 to 8 weeks and was then gradually reduced to this amount once a month. The average number of injections covering a 12-month period was 30, while the average number of injections before improvement was apparent was 4.

No unfavorable effects were observed in any of the cases. On the contrary, a general improvement in mental and physical endurance was noted in all cases. Relief from angina pectoris was obtained in each case and in none has there been any return of precordial or substernal pain, even after walking several blocks and climbing two or more flights of stairs. This symptom-free state has obtained for 6 months in some cases, and for 11½ in others.

Purely scientific study of these case reports at once

raises the objection that the value of the therapy has been judged largely upon the basis of subjective improvement. But while it is true that this objection is perhaps too often a valid one when some new therapy is reported as being highly successful in this or that disorder, the special nature of the subjective symptoms in these cases of angina pectoris renders them capable of being viewed in an objective light. It is well known how varied may be the responsiveness to the same degree of pain in different patients, but the pain of coronary occlusion is classic in its intensity and there is little doubt that the most stoic patient, gives creditable clinical information when he says that he did or he did not have this pain. Again, each of these patients reported a general improvement in mental and physical endurance and in a sense of well-being—all factors more or less subject to personal interpretation. Yet these same improvements are reported by practically every hypogonadal patient who has ever received replacement therapy with the indicated hormone and in view of this fact the stigma of subjectiveness which attaches to these observations becomes less marked. As for objective findings by which results could be judged, observable and measurable improvements in blood pressure, basal metabolic rate and skin color occurred. Of great practical importance along this line of thought is the fact that Lesser (7) substituted sesame oil for testosterone propionate, using many different variants of procedure, and was in no respect able to duplicate the results he obtained with the hormone in his cases of angina pectoris. There remain now to be considered the mechanism by which testosterone exerts its salutary influence upon these cases and the rationale of its therapeutic use in coronary artery disease.

*Role of the sex hormones in coronary occlusion.* The pain of angina pectoris or of coronary thrombosis, syndromes which are but manifestations of different degrees and types of coronary artery occlusion, is explained on the basis of myocardial ischemia arising out of the simple fact that the supply of blood to the heart muscle is grossly inadequate to the demand at a given moment. Years of painstaking research have still failed to reveal the exact mechanism of that inadequacy, but atheromatous changes in the coronary intima resulting in narrowing of the lumen or, in the absence of arterial pathology, abnormal vasomotor response are thought to be causative factors. With regard to the latter of these, it is not difficult to conceive of sluggish, inadequate, or absent dilatatory powers on the one hand or of excessive vasoconstriction on the other. Probably both phenomena, atheromatous narrowing and vasomotor instability, are etiologically concerned in some cases. But whatever the mechanism, inadequate coronary circulation is at fault and therapy must be directed at its improve-

ment, and production of vasodilation and/or promotion of collateral coronary circulation are the obvious means of affecting such improvement.

*Vasodilator properties of the sex hormones.* There is much experimental and clinical evidence in support of the contention that estrogens and androgens in some manner cause vasodilation. This evidence is reviewed by Bonnell, Pritchett, and Rardin (8) whose excellent paper on the use of the sex hormones in the treatment of angina pectoris and coronary artery disease is drawn upon at this point. These authors cite Reynolds and Foster (6) who observed dilatation of vessels in the ears of rabbits following estrogen administration. Sympatheticotropic properties have also been ascribed to these substances in that dilatation of the pupil is produced by their action. Bonnell et al further cite authorities for the following concepts: a), that estrogens exert a dilating action on the small vessels distal to arterioles; b), That estrogens are pharmacologically cholinergic, that therefore they act peripherally through enhanced acetylcholine activity, and that this same mechanism may be concerned in producing coronary dilatation; c), That estrogen deficiency in certain women produces changes in the coronary arteries and myocardium which can be corrected by estrogen replacement therapy but not by rest or by vasodilating drugs. The suggestion is advanced by Bonnell et al that "a deficiency in gonadal hormone, or an endocrine imbalance in certain individuals possessing an autonomic nervous system capable of an abnormal response, is the factor which leads to functional or organic changes in the vascular system during or after the climacteric period of life."

*Role of sex hormones in promoting collateral circulation.* Whether or not testosterone promotes development of coronary collateral circulation cannot be definitely stated but Lesser (7) speculates about this question in connection with the improvement noted in his cases of angina pectoris following their treatment with the hormone. Lesser cites authorities for the observations that anastomotic channels between the major coronary arteries develop to an increasing degree with advancing age, that the development of these channels depends upon partial or complete occlusion in one or more of the larger coronary arteries, and that the collateral circulation thus developed is in some cases entirely adequate.

*Relationship of the climacteric periods of life, coronary artery disease and sex hormone therapy.* Although no studies have been conducted on the basis of which declining gonadal hormonal function, conceded by all to be the cause of the menopause in women and by many to be the cause of a somewhat similar phenomenon in men, can be either proved or disproved as being etiologically involved in coronary



artery disease, certain facts become particularly interesting when viewed in the light of this problem. For example, it is significant to note the ages of the patients with angina pectoris reportedly benefited by testosterone, keeping in mind the age groups in which climacteric symptoms as well as those of coronary occlusion most frequently manifest themselves. Bonnell et al. noted clinical improvement in 22 of 23 patients with coronary artery disease after treating them with sex hormones. Angina pectoris had been definitely diagnosed in 21 of these patients. The group was composed of 18 men and 5 women and ages varied from 42 to 78 years, although 47 to 60 years is a more accurate representation of ages since 17 of the patients were within this age group. The 7 patients herein reported ranged in age from 52 to 75 years.

Also worthy of note is the presence or absence of associated climacteric symptoms in these patients whose chief complaints were referable to the heart. Such symptoms were present in 4 of the 5 female cases reported by Bonnell; they were present in only 3 of the 18 male cases. The 7 cases herein reported were all males and all had concomitant climacteric symptoms.

At the present time the most that can be said is that cases of angina pectoris often occur in patients whose output of sex hormone is deficient as evidenced by their exhibiting the climacteric syndrome and that sex hormone replacement therapy appears to be efficacious in the treatment of both phenomena. By virtue of its having been reported in hundreds upon hundreds of cases the subjective finding, 'improved sense of wellbeing,' takes on the clinical importance of an objective result in evaluating the efficacy of testosterone therapy in male climacteric cases. To be considered, therefore, is the possibility that this sense of wellbeing is at least a contributory factor to improvement in angina pectoris in that morbid anxiety, great emotional stress and the like are less apt to figure as precipitating causes in the attacks, and, also, in that the general tonic properties of testosterone which have been at least partly concerned in that improved sense of wellbeing have brought about an improved bodily economy which in itself militates against attacks of coronary pain. It has been suggested that the increased circulation time and the increase in basal metabolic rate caused by testosterone results in an improved vascular tone in the coronary arteries as well as in all other vessels and Steinach, Peczenik, and Kun (6) believe that the beneficial action of the sex hormones on blood circulation in true male hormone deficiency cases is due to their exerting a non-specific influence upon the blood vessels via the central nervous system.

## SUMMARY AND CONCLUSIONS

1. The beneficial results of androgen therapy in 7 cases of cardiac angina are described.
2. The effect of sex hormones upon the circulatory system and especially upon coronary circulation is discussed and the clinical investigations of others upon this subject is reviewed.
3. The frequent coexistence of coronary artery disease and the climacteric syndrome is remarked upon, directing attention to the possibility that they are both manifestations of hypogonadism.
4. Testosterone propionate appears to be a valuable therapeutic agent in angina pectoris, the effect of the hormone being mediated through its vasodilating properties acting upon the coronary circulation and/or through development of coronary collateral circulation.
5. The undesirability of unduly stimulating the libido in patients in whom vascular accidents might be precipitated is obvious. However, this should be no deterrent to sex hormone therapy provided careful selection of patients and control over dosage is practiced.

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# Some Metabolic Effects of Testosterone Implants

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**T**HORN AND HARROP (1) have shown that the administration of testosterone to normal dogs is followed by a decreased excretion of sodium and water, an effect resembling that of adrenal cortical extract. Kochakian and Murlin (2) found the nitrogen content of urine in castrate dogs diminished after the injection of androgens, while Thorn and Engel (3) noted a decrease in urinary nitrogen in normal dogs given testosterone propionate. These reports represent but a few of the recorded observations on animals.

More recently, Kenyon et al. (4) have shown that in normal men and women, and particularly in eunuchoids, the injection of testosterone propionate 'produced a reduction in the urinary excretion of nitrogen, sodium, potassium and chloride'. When the injections of testosterone were discontinued, the excretion rates returned to the pre-injection levels. Jones et al. (5) noted that the oral administration of methyl testosterone possessed 'the property of causing nitrogen, electrolyte and water retention'. The reported observations, however, have been made

over relatively short periods of time (up to 14 days) being given daily or twice daily.<sup>1</sup> Weinstein and one of us (6) have shown that the administration of testosterone pellets is followed by a very clinical response lasting for 2 to 5 months. It appeared important to determine if the effect could be determined by such metabolic studies over a longer period of time reported.

## CASE REPORT

N. B., male, age 21 years, was first seen on Oct. 1941. The past history revealed mumps in infancy, a cleft lip at 6 years of age, a bilateral herniotomy at an operation for recurrent hernia at 19 years. At 16

years of age, several injections of an unknown endocrine preparation were administered for undescended testes and at 19 years, he received 50 injections of an anterior pituitary-like preparation. The operations and injections were of no avail. His chief complaints were feminine appearance, very small genitalia, undescended testes, lack of facial and body hair and high pitched voice. He seldom had erections, libido was slight and attempts at coitus were unsatisfactory. His appearance was that of the classical eunuchoid, the lower half measurement (superior symphysis pubis to heel) was 37 inches and the upper half measurement (superior symphysis pubis to vertex) was 29 inches. The height was 66 inches, span 72.5 inches and weight 161 pounds. His appearance was feminine, the complexion smooth and the cheeks were pink. The penis was minute and hypospadias was present. There was a slight amount of pubic hair with feminine distribution. The testes were impalpable and the scrotum was small and shrunken. The visual fields were normal. Radiographs revealed a normal sella turcica but there was evidence of delay in epiphyseal ossification. The blood pressure was 132/98 mm Hg. Otherwise, the physical examination was negative.

## EXPERIMENT AND RESULTS

A diet containing 200 gm. of carbohydrate, 75 of protein, 100 of fat and 2.0 to 2.5 of sodium chloride was given daily throughout the investigation. During each period of observation, the subject was hospitalized for at least 6 days, urine voided on the last 3 or 4 days was collected in 24 hour lots and analyzed for total nitrogen by a micro Kjeldahl procedure (7), for chlorides by the Volhard-Harvey method (8), for phosphates by the uranium acetate procedure (9) and for creatinine by the method of Folin (10).

After adequate control studies were made, the patient received, intramuscularly, 50 mg. of testosterone propionate<sup>2</sup> daily for 5 days and on the 6th day, 450 mg. of testosterone,<sup>2</sup> subcutaneously implanted. Subsequent studies were made at approximately monthly intervals for 5 months. The detailed results are given in table 1. Figure 1 demonstrates graphically

<sup>2</sup> Testosterone propionate (Oreton) and the testosterone pellets were supplied through the kindness of Dr. Max Gilbert, Schering Corp., Bloomfield, N. J.

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<sup>1</sup> Since this paper was written, Sandiford, Knowlton and Kenyon (J. Clinical Endocrinology 1: 931, 1941) studied the urinary nitrogen in a eunuchoid who received intramuscularly testosterone propionate in doses of 5 to 50 mg. daily for 2 months. Throughout the entire period, the urinary nitrogen remained depressed.

TABLE 1. URINARY EXCRETION OF NITROGEN, CHLORIDES AND PHOSPHATES IN A 23-YEAR-OLD EUNUCHOID BEFORE AND AFTER INJECTION OF 250 MG. OF TESTOSTERONE PROPIONATE AND IMPLANTATION OF 450 MG. OF TESTOSTERONE

| Date        | Urine Volume cc. | Nitrogen   |         | Chlorides  |         | Phosphates |         | Creatinine |         | Remarks  |
|-------------|------------------|------------|---------|------------|---------|------------|---------|------------|---------|--|
|             |                  | gm./24 hr. | Average | gm./24 hr. | Average | gm./24 hr. | Average | gm./24 hr. | Average |  |
| November 25 | 1975             | 13.7       |         | 3.8        |         | 2.7        |         | 2.0        |         |  |
| 26          | 2450             | 13.6       |         | 2.5        |         | 2.5        |         | 2.0        |         |  |
| 27          | 2175             | 14.3       | 13.8    | 4.8        | 3.7     | 2.5        | 2.6     | 2.0        | 2.0     |  |
| 28          | 1750             | 9.9        |         | 1.4        |         | 2.1        |         | 1.6        |         | 50 mg. of testosterone propionate intramuscularly on Nov. 28, 29 and 30.                                     |
| 29          | 2105             | 11.1       |         | 2.1        |         | 2.9        |         | 1.3        |         |  |
| 30          | 1585             | 11.2       | 10.7    | 1.9        | 1.8     | 2.6        | 2.5     | 1.7        | 1.5     |  |
| December 1  | 1600             | 7.1        |         | 1.6        |         | 1.6        |         | 1.5        |         | 50 mg. of testosterone propionate intramuscularly on Dec. 1, 2. 450 mg. of testosterone implanted on Dec. 3. |
| 2           | 1555             | 8.1        |         | 1.2        |         | 1.7        |         | 1.8        |         |  |
| 3           | 1400             | 7.9        |         | 1.7        |         | 1.7        |         | 1.7        |         |  |
| 4           | 1600             | 9.6        | 9.2     | 1.6        | 1.6     | 2.4        | 2.1     | 1.7        | 1.6     |  |
| 30          | 2560             | 5.5        |         | 2.6        |         | 1.2        |         | 1.8        |         |  |
| 31          | 2600             | 9.4        |         | 2.6        |         | 2.1        |         | 2.5        |         |  |
| January 1   | 2050             | 6.8        |         | 2.1        |         | 1.4        |         | 1.7        |         |  |
| 2           | 2420             | 7.9        | 7.4     | 2.9        | 2.5     | 2.3        | 1.8     | 2.5        | 2.1     |  |
| February 15 | 2575             | 10.0       |         | 2.8        |         | 1.8        |         | 1.9        |         |  |
| 16          | 2300             | 8.9        |         | 2.5        |         | 1.4        |         | 1.3        |         |  |
| 17          | 2700             | 12.0       | 10.2    | 2.2        | 2.5     | 4.0        | 2.4     | 1.9        | 1.7     |  |
| March 28    | 2425             | 13.2       |         | 3.9        |         | 3.1        |         | 1.8        |         |  |
| 29          | 2120             | 9.4        | 11.3    | 3.9        | 3.9     | 2.3        | 2.7     | 1.3        | 1.6     |  |
| May 23      | 1950             | 9.7        |         | 5.4        |         | 3.1        |         | 2.2        |         |  |
| 24          | 1600             | 12.1       |         | 2.5        |         | 2.9        |         | 2.1        |         |  |
| 25          | 2460             | 13.1       | 11.6    | 2.0        | 3.3     | 2.9        | 3.0     | 2.5        | 2.2     |  |
| June 28     | 1860             | 12.7       |         | 4.3        |         | 3.9        |         | 2.2        |         |  |
| 29          | 1660             | 12.9       |         | 3.3        |         | 3.6        |         | 2.2        |         |  |
| 30          | 2200             | 12.0       | 12.5    | 4.8        | 4.1     | 3.6        | 3.7     | 2.6        | 2.3     |  |

the average values obtained and shows that the period of symptomatic effect of the testosterone implant (as gauged by an increase in erections and libido) parallels closely the period in which the urinary excretion of nitrogen, chlorides, and phosphates was diminished.

The clinical response to testosterone was dramatic. Approximately three months after the implantation, some 'testosterone withdrawal' symptoms appeared

which became more pronounced at the fourth month. One month later, there was a slight return of 'testosterone effect' which, however, was accompanied by no pronounced diminution in the urinary excretion of the various components studied.

#### CASE REPORT

Case 2, A. R., male, age 28 years, was first seen on June 13, 1941. The chief complaints were failure of genital development and absence of libido. The past history revealed migraine headaches for years accompanied by blurred vision, hot and cold sensations and nausea. Recurrent episodes of alternating diarrhea and constipation had occurred since 1938. One year ago, he sustained a fracture of the pelvis in an automobile accident. The physical examination revealed an infantile penis, impalpable testes and no facial but scanty axillary and pubic hair. The blood pressure was 130/80 mm. Hg. Radiographs of the skull revealed a sella turcica approximately 15 per cent above the average normal in size and a calcified pineal gland. The basal metabolic rate was 19 per cent below the average normal. There was no impairment in sugar tolerance. The visual fields were normal.

#### EXPERIMENT AND RESULTS

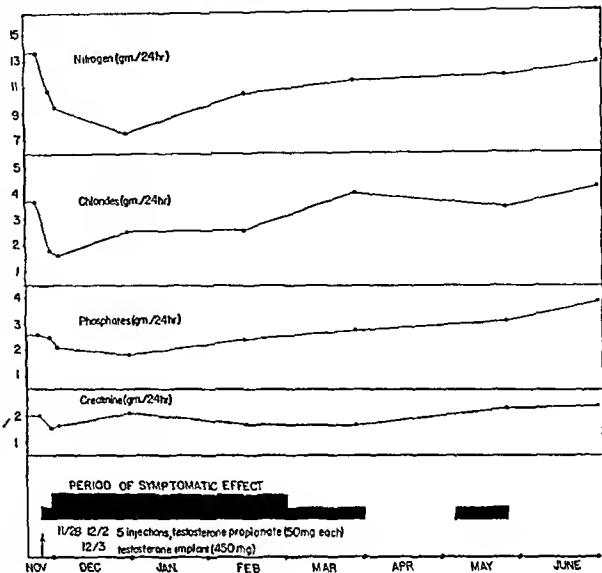
The diet, the manner of observation and the chemical procedures used were those described for case 1.

TABLE 2. URINARY EXCRETION OF NITROGEN, CHLORIDES AND PHOSPHATES IN A 28-YEAR-OLD EUNUCHOID BEFORE AND AFTER THE IMPLANTATION OF 450 MG. OF TESTOSTERONE

| Date    | Urine Volume cc.                  | Nitrogen   |         | Chlorides  |         | Phosphates |         | Creatinine |         |
|---------|-----------------------------------|------------|---------|------------|---------|------------|---------|------------|---------|
|         |                                   | gm./24 hr. | Average | gm./24 hr. | Average | gm./24 hr. | Average | gm./24 hr. | Average |
| June 26 | 1380                              | 10.3       |         | 9.0        |         | 3.1        |         | 2.9        |         |
| 27      | 1160                              | 10.0       |         | 7.4        |         | 2.8        |         | 2.9        |         |
| 28      | 1150                              | 10.4       |         | 4.8        |         | 2.6        |         | 2.6        |         |
| 29      | 1240                              | 10.0       |         | 4.0        |         | 3.1        |         | 3.1        |         |
| 30      | 1650                              | 12.4       | 10.6    | 4.6        | 5.9     | 3.2        | 2.9     | 3.2        | 2.9     |
| July 1  | 450 mg. of testosterone implanted |            |         |            |         |            |         |            |         |
| 28      | 1800                              | 9.6        |         | 3.1        |         | 1.8        |         | 2.8        |         |
| 29      | 1600                              | 8.2        |         | 4.2        |         | 2.1        |         | 2.6        |         |
| 30      | 1960                              | 10.0       | 9.2     | 5.6        | 4.3     | 2.2        | 2.0     | 3.2        | 2.8     |
| Sept. 1 | 1250                              | 8.1        |         | 4.0        |         | 2.6        |         | 2.9        |         |
| 2       | 1540                              | 7.2        |         | 5.6        |         | 2.8        |         | 2.8        |         |
| 3       | 1400                              | 7.7        | 7.6     | 5.6        | 5.0     | 2.7        | 2.7     | 2.9        | 2.8     |
| Oct. 7  | 600                               | 8.8        |         | 5.4        |         | 2.2        |         | 2.6        |         |
| 8       | 1150                              | 9.9        |         | 6.2        |         | 2.3        |         | 2.2        |         |
| 9       | 1090                              | 9.3        | 9.3     | 6.1        | 5.9     | 2.5        | 2.3     | 2.8        | 2.5     |

I EFFECT OF INJECTION OF TESTOSTERONE PROPIONATE (250 mg) and of an implant of testosterone (450 mg) on the urinary excretion of nitrogen, chlorides and phosphates in a eunuchoid, 23 years old. Life of pellet determined by excretion curve

No preliminary injections of testosterone propionate were given. Following the implantation of 450 mg of testosterone, studies were made at approximately monthly intervals for 3 months. Table 2 and figure 2 show the results obtained. The reduction in the urinary excretion of nitrogen, chlorides and phosphates was definite, though less marked than in the previous case. The clinical response was characteristic but also less pronounced than in case 1. With the onset of 'testosterone withdrawal' symptoms, the urinary findings showed a return to or near to the control levels. It may be of interest to record that during the entire period of observation, the patient was free of migraine headaches.



#### CONCLUSIONS

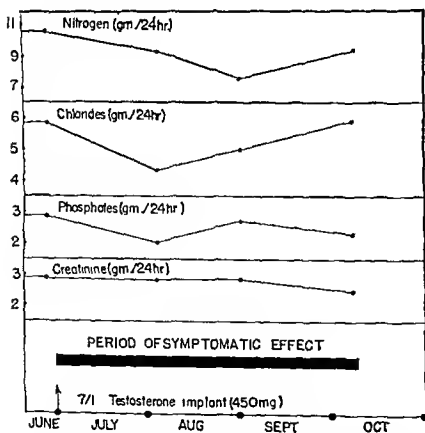
1 The observation made by other workers that the injection of testosterone propionate is followed by a reduction in the urinary excretion of nitrogen, chlorides and phosphates, is confirmed.

2 Implanted pellets of testosterone initiate and maintain a reduction in the urinary excretion of these components during a period which coincides closely with that of the clinical response.

3 These observations suggest that the 'life' of a testosterone pellet may be demonstrated by the urinary excretion of nitrogen, chlorides and phosphates.

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2 EFFECT OF AN IMPLANT OF TESTOSTERONE (450 mg) on the urinary excretion of nitrogen, chlorides and phosphates in a eunuchoid 28 years old. 'Life of pellet' determined by excretion curve

# Malignant Pheochromocytoma of the Adrenal Medulla (Paraganglioma)

Report of Case Simulating Carcinoma of the Adrenal Cortex with Secondary Adrenal Insufficiency

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## [Adrenal Medullary Tumor]

IT IS CUSTOMARY to associate pheochromocytoma of the suprarenal gland with attacks of paroxysmal hypertension in which pallor, cold, clammy extremities, palpitation, 'pounding' of the pulse, particularly in the head and neck, and severe headache are constant findings, and in which a wide variety of other signs and symptoms of sympathomimetic type are common. Such attacks may be sufficiently severe to lead to death from cerebral hemorrhage, edema of the lungs, or coma symptomatically resembling that of uremia.

Despite the fact that only a few more than 100 cases of pheochromocytoma of the adrenal have been reported in the literature (1), the above syndrome associated with paraganglioma of a benign type is well understood, although not always recognized.

The clinical findings and course of malignant forms of the condition are not so well distinguished, as only 8 cases, including that herein described, are on record, not one of which has exhibited the acute attacks of widely fluctuating blood pressure and associated sympathetic phenomena above noted.

This difference in clinical course between the benign and malignant forms of the disease, as well as the rarity of the latter type, alone justifies further case studies. In addition, the Simmonds' or Addison-like syndrome observed in the case here reported, the unilateral position and large size of the primary lesion, and the location of a metastasis adjacent to the pituitary gland are features of unusual interest.

### CASE REPORT

K. F., D 959-40, a 43-year-old white woman, was admitted to the hospital because of weakness, loss of weight and pains in or about the rectum, the chest, the left leg, and the right hip and thigh regions. For 8 to 10 years she had not felt entirely well, had complained particularly of weakness, and had noticed a gradual darkening of her skin. Five months prior to admission, sharp, intermittent, knife-like pains were experienced in several locations, a), through the rectum, aggravated by defecation and associated with obstipation; b), through the chest, most marked on deep inspiration; and c), through the left leg, increased by weight bearing or walking.

There was an amenorrhea of 4 months duration. No history of hypertension or of attacks of paroxysmal hypertension could be elicited.

On admission, her status was that of an advanced malignant cachexia (fig. 1), in which the positive findings were extreme emaciation; the facies of pain; marked gingivitis and dental caries; darkening of the skin of the face, neck, and extremities with patchy areas of pigmentation over the trunk; a blood pressure of 114/80 mm. Hg; hard, bilaterally palpable submaxillary lymph nodes; tenderness over the lower ribs on both sides; some spasticity of the abdominal wall with a visible increased 'fullness' in the right upper quadrant; a palpable, non-tender mass, contiguous with and apparently continuous with the liver, the lower border of which was felt five fingers below the costal margin; a firm, non-tender spleen extending one finger's breadth below the left costal margin; tenderness to palpation and percussion over the right sciatic notch and the head of the left fibula; hyperactive superficial and deep-tendon reflexes; a Babinski reflex present on both sides; and a negative pelvic examination.

On laboratory examination, the urine was repeatedly negative. The blood always showed a secondary anemia, a typical count revealing a hemoglobin of 66 per cent, an erythrocyte count of 3.7 million per cu mm, a leucocyte count of 8,700 per cu mm, and a differential of polymorphonuclear neutrophils 62, lymphocytes, 36, eosinophils 1, and monocytes 1 per cent respectively. The speed of sedimentation of the erythrocytes (Westergren method) was 10 mm in 15 minutes and 84 mm in 1 hour. The icteric index was 4.9, the Takata Ara reaction was weakly positive. The blood Wassermann reaction was negative.

At autopsy,<sup>1</sup> on opening the abdomen, 500 cc of bloody peritoneal fluid were encountered. The liver extended about four fingers below the umbilicus. The aorta was negative except for a few atherosclerotic patches about the sinuses of Valsalva. The visceral and parietal pleurae overlying both lungs were studded with yellowish grey sharply demarcated nodules, measuring from 1 to 20 mm in diameter and eroding and partly destroying several sections of ribs bilaterally. There was a right lower broncho pneumonia. The liver weighed 3,900 gm. Over its surface and throughout its parenchyma, there were in



Fig 1a

The basal metabolic rate was minus 22 per cent. The blood phosphatase was 3.9 Bodansky units per 100 cc. The total blood proteins were 5.8 gm per cent, with albumin 3.4, globulin 2.4, and fibrinogen 0.33 per cent, respectively. Other blood chemical constituents in milligrams per cent were: total cholesterol, 148; esters, 102; dextrose, 84; non-protein nitrogen, 50; creatinine, 2.3; calcium, 9.3; inorganic phosphorus, 5.1; sodium, 292.3; potassium, 31.4. The electrocardiographic tracings were essentially normal.

Roentgenograms of the gastrointestinal tract revealed no abnormalities. Intravenous and retrograde pyelography showed a displacement downward of the right kidney with rotation of the upper pole forward and considerable angulation at the uretero-pelvic junction (fig 2). Osteoclastic metastatic lesions were demonstrated in the following bones: The second left rib and eleventh and twelfth ribs bilaterally, the anterior inferior spine of the left ilium, the supra-acetabular region of both sides, the upper third of the shaft, head, and neck of the right femur, the skull (fig 3), particularly the frontal and parietal regions, the ninth dorsal and the first, third, and fourth lumbar vertebrae. Perirenal air insufflation failed to visualize satisfactorily the region of the right kidney or supra-renal.

Her course in the hospital was progressively downhill to the time of death 5 months after admission, with evidence from time to time of further metastases in the skin, the brain, and various bones. Her blood pressure varied from 85 to 122 mm Hg systolic, and from 70 to 82 mm Hg diastolic throughout her last illness.

<sup>1</sup> Performed by Dr. Andrea Saccone, whose cooperation we hereby acknowledge with thanks.

numerable yellowish grey nodules varying in diameter from 1 to 13 cm. The spleen weighed 440 gm, but aside from congestion revealed no pathologic change. The left kidney and adrenal together weighed 100 gm, and showed no grossly abnormal alterations. There was a large, oval mass overlying the upper pole of the right kidney, which weighed 930 gm, and measured 15 cm in its longest



Fig 1b

estimation of the estrogenic hormone in the urine, for which in a single study a high value was obtained. However, too few animals were used in the determination to warrant a satisfactory deduction and unfortunately, opportunity to repeat the bioassay with a larger number did not present itself.

The true nature of the tumor was not suspected during life, as its large size, its confinement to one adrenal, and the accompanying Addisonian syndrome are unusual features of malignant paraganglioma.

their patient, but many other features of Addison's disease were lacking. The patient had a pulmonary tuberculosis to which death was attributed.

The present patient exhibited all of the features of Addison's disease, including the excessive loss of salt from the body and a retention of potassium. As in the case of Riemer's patient, no gross or microscopic alteration of cortical tissue could be observed. Moreover, serial sections of the pituitary gland revealed no abnormalities. The observed disturbances,

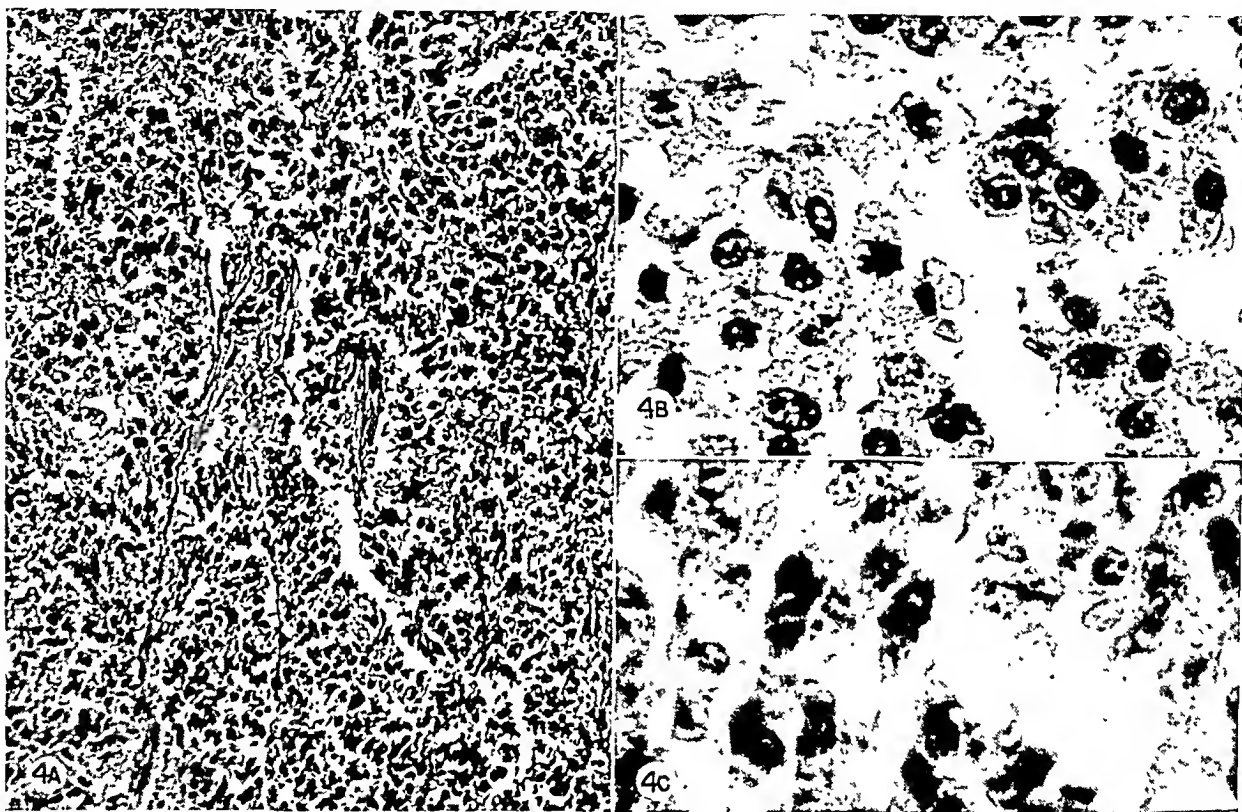


Fig. 4a. SECTION OF TUMOR ( $\times 170$ ). Note the tendency to a lobulated growth in which groups of large cells are separated by a fine, fibrovascular stroma. (H & E stain).

Fig. 4b. SECTION OF TUMOR ( $\times 930$ ). Note the marked variations in nuclear size and staining. Mitotic figures can be seen near the center of the field. (H & E stain).

Fig. 4c. SECTION OF TUMOR ( $\times 930$ ). This section was treated with Giemsa's stain (Schmorl technique). The dark granules in the cytoplasm of the tumor cells reacted to this stain in a fashion similar to that seen in the cytoplasm of the medullary cells of the normal adrenal gland simultaneously mounted and stained with them.

#### *Syndrome of Addison's Disease in Pheochromocytoma of the Adrenal*

Two reported cases of benign pheochromocytoma of the adrenal were associated with features suggestive of Addison's disease (13, 14). In Riemer's patient (13) there was a cystic tumor of the right suprarenal medulla. The cortex was intact, and neither grossly nor microscopically could any disturbance of the right or left adrenal cortex be made out. There seems to be little doubt, however, that the patient died in adrenal insufficiency. Laignel-Lavastine and Aubertin (14) mentioned a widespread melanoderma in

usually looked upon as pathognomonic of insufficiency of the cortex of the adrenal, are in the present state of our knowledge unexplainable. This is the first patient with a malignant type of pheochromocytoma to present them.

#### *Disturbances of Adrenal Cortex Other Than Addison's Disease, Associated with Paraganglioma of the Medulla*

In one instance, a chromaffinoma appears to have produced androgenic effects without any morphologic alterations being detected in the adrenal cortex

(15) Neff's patient, a girl of 16 months, in addition to the paroxysmal hypertension, developed hirsutism, acne, and hypertrophy of the labia and clitoris, all of which receded a few weeks after the removal of a 96-gram tumor. There was no gross or microscopic evidence of involvement of the adrenal cortex. These several cases in which paraganglioma has been associated with functional alterations in the adrenal cortex imply a closer relation than hitherto realized in the integration of the functions of these two portions of the gland.

*Alterations in Other Endocrine Glands Associated with Pheochromocytoma of the Adrenal*

Other glandular disturbances seen in association with paragangliomata of the adrenal medulla have included a colloid adenoma of the thyroid gland (16), a papillary adenoma-carcinoma of the thyroid without metastases (2), and diabetes mellitus (none reported since the 5 cases cited by Eisenberg and Wallerstein (2), symptoms of hyperthyroidism and hypertrichosis in a single patient, in whom, however, a diseased thyroid was not present (17), and a girl with hypertrichosis and deficient mammary development without disease in other endocrine organs (18).

*Clinical Features of Malignant Pheochromocytoma of the Adrenal Medulla*

From an analysis of the features warrant comment

a) *Sex* Three of the patients were males, 3 were females, and in the report of 2 cases the sex was not given.

b) *Age* In the 6 instances in which ages were mentioned, they were 30, 34, 43, 47, 51, and 68 years, respectively, with an average age at the time of first observation of 45.5 years.

c) *Size and location of tumor* In but 3 of the 8 cases is the size of the tumor mentioned. One of these was 5 cm in diameter, the second,  $5 \times 2$  cm, and the third, the case herein described, a nearly spherical mass 15 cm in its greatest diameter. It is interesting to note that while gangliomata of histologically benign type have been known to reach a size of 12.5 cm in diameter (19), no malignant paraganglioma of more than 5 cm in diameter has been previously described.

The paraganglioma was bilaterally situated in 5 of the 8 patients, it was confined to the right side in 1, and to the left side in 2.

d) *Symptoms and signs* Symptoms suggestive of a malignant growth were noted as much as a year prior to coming under observation (20). In one instance, weakness and increasing pigmentation of the skin were of from 8 to 10 years' standing (present

case). All of the patients, sooner or later, developed marked loss of weight with cachexia. Pain was universally present in every case and was referable either to the primary tumor or to its metastases. Epigastric distress due to encroachment of the primary tumor was mentioned in Cohn's case (quoted by Geschickter 5), and was noted in our own. Pains were reported in the region of metastases in all of the cases in which clinical history was available.

In Geschickter's patient (5), constipation and night sweats were prominent symptoms. One patient had a persistent cough and coarse râles over the bases and left upper lobe of the lungs consequent upon metastases to that organ.

Blood pressure is mentioned in 3 patients. In none of them was there hypertension, and in King's (20) and our patient actual hypotension existed. In no instance was there any intimation that bouts of paroxysmal hypertension existed or had existed at any period of the patient's life. Inasmuch as such attacks are looked upon as pathognomonic of paraganglioma, it seems important to emphasize not only their complete absence in the malignant forms, but also their failure to occur in slightly less than 50 per cent of the benign cases (2).

A palpable mass was found on the right side in two patients (present case and 2), and on the left in one (5).

Widespread metastases were visible and palpable in the skin in two instances (20 and present case).

e) *Metastases* The regional lymph nodes were involved in all patients, and were the only point of metastasis noted in one (Cohn's case cited by Geschickter 5). Lymph nodes of the thoracic cavity were invaded in 5 instances, and involvement of the lymph nodes in the region of other metastases has been variously recorded. The liver was enlarged and the seat of secondary growth in at least 4 of the 8 patients (2, 20, 21, present case). Widespread metastases to bony structures have been observed (2, 20). The vertebrae, the ribs, the pelvis, the cranium, and the femora have been involved with a frequency somewhat in the order named. Three patients exhibited widespread metastases to the lung (2, 20, present case). The pleurae (22, present case) and the skin (20, present case) were the seat of secondary malignancy in two instances each. Among other locations of metastatic invasion, the intestines (2) and the kidney (5) have been mentioned.

SUMMARY

1 The eighth reported case of malignant paraganglioma of the adrenal medulla with widespread metastases is described.

2 The absence of bouts of paroxysmal hypertension in patients with the malignant form of paraganglioma is emphasized.



3. The right adrenal medulla was the only endocrine structure to show gross or microscopic changes of a pathologic nature.

4. Unusual features observed in the present instance of paraganglioma of the adrenal medulla included an Addisonian-like syndrome in the presence of histologically normal pituitary and adrenal cortical tissues; the strictly unilateral adrenal involvement; and the large size of the primary tumor.

5. The major features of malignant pheochromocytomata of the adrenal are summarized.

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# Potassium Tolerance Test as an Aid in Diagnosis of Adrenal Insufficiency

## [Adrenal Insufficiency]

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THE TYPICAL SIGNS AND SYMPTOMS of Addison's disease rarely become manifest until extensive damage has been done to the adrenal cortex. It is not the well defined adrenal cortical failure that tests the diagnostic acumen of the physician, but the borderline case. A procedure to discern early hypoadrenia would be of inestimable value. At present there are a few procedures which have been advocated as an aid for the early diagnosis of hypoadrenia. Wilder (1) described a diagnostic test for the determination of adrenal cortical failure which is based on the concentration of the urinary chloride after the intake of sodium, potassium and water has been controlled for a period of 3 days. However, its value in early cases of hypoadrenia is questionable, since it must be done in a hospital and it frequently makes a patient who has Addison's disease severely ill. The findings furthermore are often indecisive in the indefinite case. Robinson, Power and Kepler (2) described two new procedures to aid in the recognition of Addison's disease. These tests are based on the facts that a), in most cases of Addison's disease, the kidneys continue to secrete fairly concentrated urine even after water has been ingested, b), patients suffering from Addison's disease tend to excrete excessive amounts of sodium chloride but retain urea. The authors explain that these procedures are particularly useful in eliminating insufficiency of the adrenal cortex as the cause of fatigue states. They do not advocate these procedures as a means of proving the function of the adrenal cortex to be normal. Thorne (3) suggests that a good diagnostic method is the therapeutic test.

This paper will devote itself to a discussion of the potassium tolerance test, which was devised by Zwemer (4) in 1936 to determine mild adrenal cortical insufficiency.

The adrenal cortex is affected in numerous diseases and conditions (5). Severe burns, food poisoning and a variety of acute infections, according to Aschoff,

Goldzieher and Dietrich, will cause hyperemia, edema and focal necrosis in the adrenal cortex. Diphtheria and scarletina cause marked injury to the cortex but not to the medulla. Following severe trauma and secondary shock the adrenal cortex becomes rapidly depleted of lipid, and cellular necrosis appears. In all of these injuries and diseases the plasma potassium is high.

Zwemer and Truszkowski believe that the symptoms of adrenal cortical insufficiency are in many respects identical with potassium poisoning and that a disordered potassium metabolism is the primary defect of adrenal cortical insufficiency. It is possible to postulate that the adrenal cortex is affected by many more conditions than is at present known, so that a positive potassium tolerance curve may be obtained in diverse conditions.

In experimental adrenal insufficiency in animals there is an increased susceptibility to exogenous potassium (6). The plasma potassium of normal animals is not affected by the ingestion of potassium. In adrenal insufficiency in human beings there is a rapid and very considerable rise in the plasma potassium after the ingestion of 10 mg. of potassium per pound of body weight (7). The test is performed as follows: From a fasting patient, capillary or arterial blood is taken and a potassium drink having the equivalent of 10 mg. of potassium per pound body weight is given. Blood is then taken at the end of 30, 60 and 120 minutes and the potassium of the plasma is determined. The resultant curve in a normal individual will be flat or show no more than a 10 per cent rise. Zwemer (8) found the greatest value of this test in cases of asthenia and hypotension. Patients with these symptoms having a positive potassium tolerance curve, treated with adrenal cortical extract, had a complete alleviation of their symptoms. Patients with a normal potassium tolerance curve, with the same symptomatology, had no relief with adrenal cortical extract.

Recently, Green, Levine and Johnston (9) reported

the value of determining the potassium tolerance curve. They came to the conclusion that the test was not diagnostic since they found abnormal curves in cases of bromism, neurasthenia and nephritis, while in two cases of Addison's disease the curve was normal. They mention, however, that their technique was different from Zwemer's. Zwemer specifically states that the blood must be arterial, since the potassium content of venous blood varies because potassium is an intracellular substance and so will vary in the venous blood.

We have performed 43 tests following Zwemer's technique on 42 patients (as shown in the accompanying table), and have obtained 12 abnormal curves.

TABLE 1. POTASSIUM TOLERANCE IN VARIOUS TYPES OF PATIENTS

| Diagnosis                  | Number of Cases | Potassium Tolerance Curve |          |
|----------------------------|-----------------|---------------------------|----------|
|                            |                 | Normal                    | Abnormal |
| Hirsutism                  | 16              | 15                        | 1        |
| Allergy                    | 6               | 5                         | 1        |
| Menopause                  | 3               | 3                         |          |
| Pituitary adenoma          | 3               | 1                         | 2        |
| Basophilism                | 2               |                           | 2        |
| Addison's disease          | 2               |                           | 2        |
| Nephritis                  | 2               | 2                         |          |
| Asthenia                   | 2               |                           | 2        |
| Obesity                    | 1               | 1                         |          |
| Hypertension               | 1               | 1                         |          |
| Male climacteric           | 1               |                           | 1        |
| Metrorrhagia               | 1               | 1                         |          |
| Adrenal cortical carcinoma | 1               | 1                         | 1        |

CASE REPORTS

Case 1, L F. A 44-year-old white male was admitted to the hospital on 4/20/40 with symptoms of weakness and dizziness of 7 months duration. In 1938 he had been treated for bilateral pulmonary tuberculosis with a right phrenic crush. On admission physical examination revealed a thin brownish-looking male complaining of weakness, tiredness and dizziness. There was brown pigmentation over the entire body. Blood pressure was 88/65 mm. Hg. The electrocardiogram and intravenous pyelogram were normal. The basal metabolic rate was -2, the blood urea 9.8, uric acid 6.3, cholesterol 366 mg. %, and the sodium was 314 mg; this latter dropped to 297. A roentgenogram of the lungs showed the presence of a productive type of apical tuberculosis without cavitation. The diagnosis was Addison's disease and he was given a high salt and low potassium diet with striking subjective improvement.

Case 2, C S. A 40-year-old white female was admitted to the hospital on 1/27/40 with complaints of progressive weakness and skin pigmentation for the past two years. She had marked emotional lability. Physical examination revealed no gross pathology. The blood pressure was 98/68 mm. Hg and the sodium was 292 and 295 mg. on two different occasions. No treatment was given.

| Potassium Tolerance, mg % |      |         |      |
|---------------------------|------|---------|------|
| Case 1                    |      | Case 2  |      |
| Fasting                   | 21.3 | Fasting | 18.2 |
| ½ hr.                     | 26.5 | ½ hr.   | 21.0 |
| 1 hr.                     | 30.3 | 1 hr.   | 22.2 |
| 2 hr.                     | 32.4 | 2 hr.   | 22.2 |

These two cases of Addison's disease showed positive potassium tolerance curves as was expected.

Case 3, R J. A 36-year-old white female entered the Endocrine Clinic with complaints of weakness, tiredness and dizziness. Physical examination revealed no gross abnormalities. The blood pressure was 100/60 mm. Hg and there were a few pigmented spots on the buccal mucosa and face. She was put on a high salt diet with remarkable relief of her complaints. The blood pressure rose to 120/74 mm. Hg. Cessation of salt administration was followed by recurrence.

Case 4, M.G., a white adult female entered the Endocrine Clinic with complaints of amenorrhea, backache, headache, tiredness and drowsiness. Physical examination revealed a small adenoma of the thyroid and some yellowish areas of pigmentation on the face. Blood pressure was 114/70 mm. Hg, and sodium 306 mg. She was put on a high salt diet with excellent improvement in her general well-being.

| Potassium Tolerance, mg % |      |         |      |
|---------------------------|------|---------|------|
| Case 3                    |      | Case 4  |      |
| Fasting                   | 16.3 | Fasting | 22.0 |
| ½ hr.                     | 22.0 | ½ hr.   | 22.9 |
| 1 hr.                     | 22.2 | 1 hr.   | 23.5 |
| 2 hr.                     | 22.2 | 2 hr.   | 25.0 |

These are two cases of asthenia that are probably early cases of hypoadrenia. They both felt very much better when put on a high salt diet.

Case 5, G.F., a 53-year-old white female was admitted to the Endocrine Clinic because of acromegalic facies. Her appearance had changed completely in the past 3 years. At present she was complaining of headaches, weakness and tiredness. Physical examination revealed an obese woman without demonstrable pathology. Roentgenograms of the sella turcica showed a broadened sella with loss of density in the bony markings of the floor; the posterior clinoid processes were thin. A hyperostosis frontalis was present. The basal metabolic rate was +4, cholesterol 305, calcium 11, phosphorus 3.8 mg. %. The blood sugar leads in a glucose tolerance test were 83, 162, 120, 108 mg. % after 0, ½, 1 and 1½ hours respectively. The visual fields showed concentric narrowing. She received roentgen-ray therapy to the pituitary with improvement in her headaches though she still complained of tiredness and weakness.

Case 6, L W., a 49-year-old white female entered the Endocrine Clinic complaining of headaches, dizziness and attacks of weakness. In 1935 roentgenograms showed enlargement of the sella turcica with erosion of the dorsum sellae. She received at that time 4,240 r of roentgen therapy. In April, 1939, the skull showed no change. In March, 1940 she entered the Endocrine Clinic with the above complaints. Roentgenograms showed further enlargement of the sella. 2,560 r roentgen therapy was given.

The visual fields were normal. There was slight hirsutism of the arms which was first noticed 7 years ago. Blood pressure was 150/110 mm Hg. The BMR was +13 and sodium 324 mg %.

Potassium Tolerance, mg %

| Case 5           |      | Case 6           |      |
|------------------|------|------------------|------|
| Fasting          | 17 1 | Fasting          | 17 4 |
| $\frac{1}{2}$ hr | 18 2 | $\frac{1}{2}$ hr | 16 6 |
| 1 hr             | 20 4 | 1 hr             | 19 4 |
| 2 hr             | 19 5 | 2 hr             | 19 5 |

These two cases of pituitary adenoma were probably in a period of relative pituitary failure so that we can postulate a depression in the production of the adrenotropic factor causing a secondary adrenal cortical insufficiency.

Case 7, M M. A 46-year-old white male entered the Endocrine Clinic on Oct. 10, 1940, with the complaint of generalized weakness. Past history was negative except for attacks of gonorrhea in 1919 and 1923. In April of 1940 he had an attack of angina pectoris which was not severe and he continued to work. However, because of weakness he stopped working. He was in the Veterans' Hospital for 4 weeks. On admission he complained of generalized weakness, impotency and loss of libido. His appetite was good and he had gained 20 pounds in the past year. Physical examination revealed a well developed plethoric male. His heart was enlarged to the left and right with no murmurs. His weight was 222 pounds, height 68 $\frac{1}{2}$  inches, span 68 $\frac{1}{4}$  inches, lower measurement 35, and the blood pressure was 190/120 mm Hg. Cardiogram showed myocardial involvement. The BMR was +1, the blood sugar levels in a glucose tolerance test were 121, 193, 266, 157 mg % at 0,  $\frac{1}{2}$ , 1 and 1 $\frac{1}{2}$  hours, respectively with a spilling of sugar after 1 and 2 hours. Calcium was 9.9 and phosphorus, 3.5 mg %. Test of the urine for prolan and estrin were negative. Roentgenograms of the skull showed a densely calcified pineal. He did not return for treatment.

Case 8, S P. A 25 year old white female entered the Endocrine Clinic on 11/22/40 with a chief complaint of obesity which had failed to decrease with diet. Seven months ago the menses became delayed, occipital head aches started and hair on the face started to grow. Physical examination revealed an obese female with striae over the abdomen and near the axillae. Heart and lung findings were negative. Fingers were short. Blood pressure was 160/120 mm Hg. Weight was 284 pounds, height 66 inches, span 68 inches, and lower measurement was 33 $\frac{1}{2}$  inches. The eye grounds and visual fields were normal. Roentgenograms of the sella and intravenous pyelogram were normal. Urine analyses showed that prolan was present and estrin to the amount of 4 R U. BMR was +7, cholesterol 368 mg %, sodium 322 mg and blood sugar values in a glucose tolerance test were 94, 131, 158, 124 mg % at 0,  $\frac{1}{2}$ , 1 and 1 $\frac{1}{2}$  hours, respectively. She was given estradiol benzoate, 2,000 R U twice weekly.

Potassium Tolerance, mg %

| Case 7           |      | Case 8           |      |
|------------------|------|------------------|------|
| Fasting          | 19 8 | Fasting          | 20 0 |
| $\frac{1}{2}$ hr |      | $\frac{1}{2}$ hr | 22 9 |
| 1 hr             | 24 2 | 1 hr             | 22 9 |
| 2 hr             | 20 0 | 2 hr             | 24 2 |

In these two cases of basophilism there is no evidence of any adrenal cortical insufficiency.

Case 9, M H. A 44 year old white male diabetic entered the Endocrine Clinic on 10/21/40 because of impotency of 8 months duration, weakness and tiredness. Physical examination revealed a slender hirsute individual with well developed genitalia and brown pigmented areas on the face. Blood pressure was 135/40 mm Hg, height, 67 inches, weight, 143 pounds, span, 67 inches, the BMR, +4. Skull roentgenograms were normal. He received thyroid medication without improvement, then placebos and salt. He stated that he felt considerably better. He was then given methyl testosterone, 30 mg daily with no improvement.

Case 9, K Tolerance mg %

|                  |      |
|------------------|------|
| Fasting          | 20 0 |
| $\frac{1}{2}$ hr | 23 2 |
| 1 hr             | 23 5 |
| 2 hr             | 23 0 |

Here again there is no definite evidence of any adrenal cortical insufficiency although the good response to salt therapy is indicative of adrenal cortical involvement.

Case 10, B K. A 26 year-old white female was admitted to the hospital on 10/2/40 with complaints of hirsutism, amenorrhea and pain in the right costovertebral region for 3 years. On Dec. 21, 1938, she had been operated on and an adrenal carcinoma had been removed. On admission an intravenous pyelogram showed an extrinsic deformity at the superior angle of the right kidney. Roentgenograms of the lungs showed metastatic infiltration. On October 14 the blood pressure was 170/112 mm Hg. On October 20 the patient suddenly went into collapse simulating an Addisonian crisis. The blood pressure at this time was 72/50 mm Hg. The patient died Nov. 1, 1940.

Case 10, K Tolerance, mg %

|                  | A    | B    |
|------------------|------|------|
| Fasting          | 20 0 | 19 0 |
| $\frac{1}{2}$ hr | 19 2 | 19 9 |
| 1 hr             | 20 0 | 22 2 |

Here we find a patient with an adrenal cortical carcinoma had a normal potassium tolerance curve, but as soon as an adrenal failure set in, the tolerance curve became abnormal.

Case 11, M Z. A 12 year old white boy suffering from asthma and allergic rhinitis who had been treated unsuccessfully in the Allergy Clinic entered the Endocrine Clinic. The BMR was -18 and he was given thyroid, 0.5 gram daily and felt better for a time but attacks of asthma started again. He was then given desoxycorticosterone<sup>1</sup> with improvement. Treatment was voluntarily stopped and asthmatic attacks recurred. No improvement was noted when treatment was repeated.

Case 11, K Tolerance, mg %

|                  |      |
|------------------|------|
| Fasting          | 18 2 |
| $\frac{1}{2}$ hr | 19 3 |
| 1 hr             | 20 5 |
| 2 hr             | 22 9 |

There is no direct evidence that the adrenal cortex is involved in the allergic states. However, when histamine or anaphylactic shock is induced in animals the adrenal cortex shows necrosis and loss of lipid in the cells. The tissues of adrenalectomized animals are also high in histamine content. So if we assume, as has been suggested, that the allergic state is due to a liberation of histamine, it is possible that a diminished cortical activity is present.

*Case 12, F.K.* A 21-year-old white girl entered the Endocrine Clinic on 9/21/40 with the complaints of hirsutism and weakness. Menses began at 11½ years, were irregular and lasted 4 to 5 days. Physical examination revealed a tall, thin, angular female with facial hirsutism and acne. Blood pressure was 120/68 mm. Hg, height 68½ in., weight 120 lb, span 66 in., and lower measurement 37½ in. The clitoris was slightly enlarged and there was a male escutcheon. The uterus was small. Epiphyseal union was normal. The B M R was -10, cholesterol 229 mg. %, prolan negative, estrin 2 R.U. Blood sugar values in a glucose tolerance test were 81, 168, 108, and 73 mg. % after 0, ½, 1 and 1½ hours, respectively. Intravenous pyelogram was normal. She was given desoxycorticosterone with no improvement.

| Case 12, K Tolerance, mg % |      |
|----------------------------|------|
| Fasting                    | 16.6 |
| ½ hr.                      | 22.2 |
| 1 hr.                      | 18.2 |
| 2 hr.                      | 16.6 |

In this case, as has been suggested, we can assume an overactivity of the androgenic function of the adrenal. The gland presumably functions patho-

logically and an excess of androgenic substance is liberated causing secondary masculine changes or there is a conversion of the normal hormone to an abnormal one which assumes masculinizing activity at the expense of the salt-regulating activity.

#### CONCLUSIONS

We have noted that the potassium tolerance test gives a specific response in Addison's disease and in other conditions in which there is a possible adrenal cortical insufficiency. At present we do not believe this test to be too specific and it might be simpler to use salt as a therapeutic test. The only advantage of the potassium tolerance test is in its objectivity.

We hope in the near future to report on a large series of cases of asthenia, since we believe that this test is of definite value in this type of ailment.

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<sup>1</sup> The desoxycorticosterone used was supplied by the Schering Corporation, Bloomfield, N. J.



# Clinical Report of the Treatment of A Case of Pemphigus with Desoxycorticosterone Acetate

## [Adrenals and Pemphigus]

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ANY DEFINITION of pemphigus has heretofore included in its formulation three principal characteristics. It has been described as an acute or chronic inflammatory disease of the skin, of unknown etiology, that often terminates fatally. In the light of recent investigation, this formulation requires revision. Although the full etiology of pemphigus remains undetermined, important contributory factors in the form of adrenal involvement have been demonstrated. Secondly, while the cutaneous manifestations still remain outstanding, fundamental alterations in salt and water metabolism have been demonstrated. Lastly, treatment aimed at the metabolic disturbances has produced remissions and cures of the manifestations of pemphigus.

Talbott (1, 2) and his co-workers investigated intensively a group of 24 cases of pemphigus from the metabolic point of view. Of these 24 cases, 10 were acute pemphigus and manifested the most outstanding and consistent changes in salt and water metabolism. These changes were: a), An invariable lowering of the serum sodium chloride, the deviation from the normal being associated with the mass of skin involved and the severity of the clinical condition; b), Lowering of the serum protein with reversal of the albumin globulin ratio; c), Increase in the plasma volume and total interstitial fluid. The results of kidney function studies were negative, indicating that these metabolic disturbances occurred in the absence of tubular or glomerular damage.

Since all of the serum changes observed, except for the serum protein variations, can be found in adrenal insufficiency, treatment was aimed at rectifying this deficiency. The 10 cases of acute pemphigus were divided into two groups of 5 each. The control group received at one time or another, almost every form of therapy, ranging from whole blood transfusions to parenteral liver, sulfanilamide, yeast and cod liver oil, from salyrgan and ammonium chloride to Fowler's solution, ascorbic acid and thiamin chloride. All 5 of these patients died.

The other 5 cases were treated with adrenal cortex extract and sodium chloride. In this group, two cases developed remissions which have lasted in one for 3 1/2 years and in the other for 3 years. In the other three cases, remissions were also induced. However, relapses followed cessation of therapy, and resumption of therapy after one or more relapses eventually was ineffective.

Finally, postmortem examination of 3 of the patients with acute pemphigus revealed, in 2 of the 3, gross adrenal damage.

Whatever the underlying causes may be, there can be little doubt that the alterations in salt and water metabolism in this disease, play a fundamental rôle. Any treatment aimed at returning these fluid and salt changes to normal, if successful, should play an important part in ultimate complete recovery.

In the following clinical case report<sup>1</sup> we wish to describe a case of acute pemphigus treated with these principles in mind.

### CASE REPORT

G B, a 61-year old male, an operator at dresses, was admitted to the Bronx Hospital Dec. 9, 1940 with complaints of itching and a rash of 2 weeks' duration. His family history and past history were essentially negative. His present illness began two weeks prior to admission with itching and rash of the upper back. As a result of itching and constant scratching, the rash spread, soon involving the entire body. The patient gave no history of taking any medication except alophen, which laxative he had been taking nightly for the previous 2 to 3 years.

On admission, the patient was found acutely ill, in anguish as a result of itching and furious scratching. The positive physical findings were: a), a coarse tremor of the right hand and forearm of one year's duration; b), erythematous, eczematoid skin eruption with patches all over the body except for the head. There were numerous bullae on the inflammatory areas. The bullae were tense and contained clear fluid. There were no oral lesions. The temperature was 101° F, hemoglobin 94 per cent, red blood cells 4,800,000, white blood cells 11,600 with 85 per cent

<sup>1</sup> We are grateful to Dr. Samuel Feldman for permission to investigate and treat this patient.

polymorphonuclear leucocytes. Blood Wassermann reaction was negative. The values for blood sugar, blood urea and blood creatinine were essentially normal.

The first differential diagnosis lay between a bullous erythema multiforme, possibly on the basis of the drug allophen, and pemphigus.

The patient was immediately started on potassium permanganate baths, colonic irrigations, low protein diet, salol and ichthyl and calamine lotion. The itching continued and many new bullae appeared on the body. Ten days after admission the inflammatory condition of the skin had partially subsided and many new bullae were appearing on a non-inflammatory base. The diagnosis of pemphigus appeared definitely justifiable at this time. The patient was, therefore, given 1 gram of sulfathiazole every 6 hours. Six days later, because the sulfathiazole concentration was only 2 mg. per cent and there had been no change in the patient's condition, the dosage was increased to 1 gram every 4 hours. The temperature continued to fluctuate between 99 and 101° F. Ten days after starting the sulfathiazole therapy, the patient's condition appeared worse, and there were many new bullae.

Sulfathiazole was, therefore, discontinued and the patient was given intravenous .9 per cent calcium gluconate and sodium arsenate solution. His condition remained unchanged, however. Therefore, after 2 weeks of therapy the arsenate and calcium gluconate were discontinued and only Balsam of Peru and zinc oxide were used locally on the body and legs.

Examination of the fluid of the bullae at this time showed a sodium chloride content of 528 mg. per cent. Because of the apparent disturbance of the fluid and salt metabolism, the patient was given at this point, 9 weeks after the onset of his illness, desoxycorticosterone acetate.<sup>2</sup> Five mg. of desoxycorticosterone acetate were given 3 times daily for 3 weeks and then the drug was reduced to 5 mg. daily. Within a week after starting this therapy the patient began to show a slow but steady improvement and at the time when the dosage was decreased there was marked improvement, all scratching and itching having ceased and only occasional rare new bullae appearing. After 5 weeks of treatment, no new bullae appeared at all. During this period of desoxycorticosterone acetate therapy, the blood pressure was maintained between 100/60 and 110/70 mm. Hg. Several furuncles and carbuncles had appeared earlier and these were treated with shortwave diathermy. Seven weeks after beginning the desoxycorticosterone acetate therapy, the patient was discharged in good condition.

He was seen in the Endocrine Clinic 6 weeks later, at which time his condition was good, no new bullae having appeared. His blood pressure was 160/85 mm. Hg. Five weeks later, a total of 11 weeks following cessation of therapy, occasional small blebs began to appear on his arms. He was, therefore, given 5 mg. of desoxycorticosterone acetate 3 times weekly and within 2 weeks there were no more blebs. Treatment was continued for another 2 weeks and was then discontinued.

<sup>2</sup> The desoxycorticosterone acetate (Cortate) was supplied through the courtesy of Dr. Max Gilbert of the Schering Corporation, Bloomfield, N. J.

Ten days later blisters began to appear once more on the upper and lower extremities. The patient was observed without therapy for 10 weeks. During this period 2 to 3 fresh blebs continued to appear daily. Systolic pressure was maintained between 155 and 160 mm. Hg.

At the end of this period of observation the patient was given once again desoxycorticosterone acetate, receiving 5 mg. twice weekly. After the first 10 days no more blebs appeared. A total of six injections were given and the desoxycorticosterone acetate was then discontinued. In the period of 5 months since the final cessation of treatment, there have been no new blebs. Blood pressure is 170/100 mm. Hg. Examination of the skin of the abdomen shows numerous small brown pigment spots at the site of the former blebs.

#### DISCUSSION AND CONCLUSION

The impressive response of this patient to adrenal hormone therapy is additional support of the work of Talbott (1). One important difference should be noted. Talbott observed that relapses proved progressively resistant to therapy until death intervened. In our case relapses were mild and were controllable within 10 days by the resumption of adrenal cortex hormone in small doses. Whether this depends on the use of desoxycorticosterone acetate instead of the adrenal cortex extract, needs further investigation.

It is apparent that the development and maintenance of a state of altered permeability and deranged salt and water metabolism plays an important rôle in the clinical course of pemphigus. Winter and Hartman (3) have demonstrated a water shift in the muscles of the adrenalectomized animal. Talbott (1) et al. (2) have found alterations in salt and water metabolism in 10 cases of acute pemphigus, similar to the alterations observed in adrenal insufficiency. With these findings in mind, it would appear consistent and logical to undertake the treatment of the manifestations of pemphigus as the manifestations of an adrenal insufficiency. It would appear to be desirable to use the extract of the whole adrenal cortex for this purpose. However, in our case, desoxycorticosterone acetate was used because therapy was aimed directly at the alteration in salt and water metabolism and, therefore, the most potent available fraction for the purpose was used.

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# COMMUNICATIONS TO THE EDITORS

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## Inhibition of Lactation

### II. Oral Use of Methyl Testosterone

IN A PREVIOUS COMMUNICATION<sup>1</sup> we reported on the percutaneous use of the male sex hormone, for the inhibition of lactation. We found that it was effective in 68 per cent of our cases resulting in a) a diminution in the degree of lactation, b) in the lack of breast engorgement and c) in the absence of pain. The method of administration however was bothersome to the nursing staff. With the advent of methyl testosterone we wished to determine whether equally good results could not be obtained by its oral administration.

Twenty five cases from the obstetric service of the Bronx Hospital were therefore treated with tablets of the male sex hormone. Each tablet contained 10 mg of methyl testosterone and was administered beginning 40 hours after delivery according to the method of Duffy and Corsaro.<sup>2</sup> The patients were given three 10 mg tablets 3 times a day for 3 days, a total of 270 mg of methyl testosterone.

\* Of importance was this fact, that methyl testosterone was given at the beginning of lactation, that is on the second day after delivery.

There was complete inhibition of lactation in 23 of the 25 cases (91%). Two patients did not respond to the above amount and showed no response to additional therapy. Tight breast binders, catharsis and rigid limitation of fluids were purposely omitted and were found not to be required.

#### SUMMARY

Methyl testosterone, orally, can be substituted for testosterone propionate, parenterally or percutaneously, for the inhibition of lactation in the post partum patient.

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\* The methyl testosterone (Neo Hombreol M) used in all cases in this paper was supplied through the kindness of Dr M C James of Roche Organon Inc. Nutley New Jersey

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<sup>1</sup> FLEISCHER A J AND J I KUSHNER *J Clinical Endocrinology*

<sup>2</sup> 407 1941

<sup>2</sup> DUFFY P V AND J CORSARO *J Am Med Assoc* 116 33

1941





# Abstracts of

## CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. Collaborators: E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLIN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, EMMERICH VON HAAM.

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### ENDOCRINE GENERAL

ANONYMOUS.

Antihormones. *Lancet* 242: 203. 1942.

This review points out that if animals are given repeated injections of certain hormones, especially A P extracts, they become insensitive to the physiological action of the hormones. Collip and Anderson (1934) demonstrated that the refractory state depends upon inhibitory substances in the serum which they called antihormones. Since then investigators have asked whether antihormones are antibodies in an immunological sense or whether they are antagonistic hormones. Evidence has been presented (9 investigations cited) to support each view but the stronger evidence is in favor of the conclusion that antihormones are true antibodies. The controversy will not be settled until there is a visible *in vitro* reaction of the antihormone with the hormone (antigen) which has stimulated its formation.—J. B. Paton (courtesy Biol. Abstracts).

BACHMAN, C.

The normal excretion of estrogen and pregnanediol preceding normal parturition. *Am. J. Obst. & Gynec.* 42: 599, 1941.

Urinary estrogen and pregnanediol excretion was studied frequently during latter part of pregnancies of 6 women. These data did not permit a prediction of the date of labor.—E.C.H.

CORNBLEET, T., AND B. BARNES.

Androgen and the xanthomatoses. *Arch. Dermat. & Syph.* 44: 248. 1941.

Seven subjects with a variety of lipidoses excreted normal quantities of urinary 17-keto-steroids as measured by a modification of the method of Dingemans.—I. C. Winter (courtesy Biol. Abstracts).

FLUHMAN, C. F., AND K. M. MURPHY.

Endocrine factors in secondary amenorrhea. *Am. J. Obst. & Gynec.* 42: 565. 1941.

Clinical correlational studies of 73 women, aged 15 to 38 years, with secondary amenorrhea are reported. Forty-four per cent of 66 patients had B.M.R.'s ranging from -10% to -27%. Blood estrogens were studied in 52 patients: negative results were obtained in only 2 patients; cyclic increases were encountered in 46 patients. Excessive blood gonadotropins were found in 20% of 34 women.—E.C.H.

GRAY, L. A.

Clinical evaluation of equine gonadotropin. *Am. J. Obst. & Gynec.* 43: 387. 1942.

Results of equine gonadotropin therapy of 83 patients are reported: of 16 patients with amenorrhea or infrequent bleeding treated, 12 experienced episodes of bleeding during therapy, which, in 6 patients, were associated with varying secretory responses of the endometrium; of 27 patients with prolonged and/or excessive bleeding from estrogenic endometrium treated, 5 patients experienced varying degrees of secretory alteration in their endometrium and 11 patients noted some improvement in bleeding; of 30 patients with dysmenorrhea treated, 21 were judged to have been improved; of 10 men with decreased seminal values treated, 5 were judged improved.—E.C.H.

GREENE, R. R.

Reactions to estrogens. *Am. J. Obst. & Gynec.* 42: 858. 1941.

Thirty-nine menopausal patients, 37 of whom had been treated previously with diethylstilbestrol propionate, were treated with estradiol carbethoxylate. The incidence of undesired and untoward responses was essentially the same from each medication.—E.C.H.

HOLLENBECK, Z. J. R., AND P. J. REEL.

The use of stilbestrol in the management of the menopause. *Am. J. Obst. & Gynec.* 43: 331. 1942.

119 patients were treated. Dosages ranged from 0.05 mg. to 2 mg. daily for oral use and from 0.1 mg. to 15 mg. per week for parenteral use. Postmenopausal bleeding occurred in 2 instances and nausea in 23 patients.—E.C.H.

IVY, A. C.

Internal secretions of the gastrointestinal tract. *J. Am. Med. Assoc.* 117: 1013. 1941.

The endocrine secretions discussed are gastrin, secretin, cholecystokinin, enterogastrone, enterocrinin, villikin, and duodenin. The evidence for these possible secretions is reviewed.—C.P.

KUNSTADTER, R. H.

Adiposogenital dystrophy. *J. Am. Med. Assoc.* 117: 1947. 1941.

The author emphasizes that not all obese children outgrow their fatness, and not all children with hypogenitalism improve spontaneously. The history, physical examination, and laboratory tests must be evaluated properly

before instituting endocrine therapy. The objective therapeutic response to thyroid may be necessary to establish a diagnosis, although congenital absence or disease of certain elements of the anterior pituitary may nullify the effect of thyroid even in a hypothyroid child. Treatment of all forms of childhood hypothyroidism should be early, adequate, and persistent —C P

LASS, P M

The inhibition of lactation during the puerperium by methyl testosterone. *Am J Obst & Gynec* 43 86 1942

Twenty five patients were treated. The usual regime of therapy embraced the oral administration of 30 mg of methyl testosterone every 3 hours for 5 doses, treatment beginning 36 hours after delivery, subsequently 20 mg were given every 3 hours for an additional 5 doses. It is reported that this treatment was effective in drying up breasts —E C H

NOVAK, E

Gynecologic problems of adolescence. *J Am Med Assoc* 117 1950 1951

The problems discussed are abnormal height, dysmenorrhea, amenorrhea, functional bleeding, obesity, hirsutism, and breast abnormalities —C P

PAINE, A K

Pathology of the embryo and abortion. *Am J Obst & Gynec* 43 245, 1942

This deals in general with the causes and treatment of abortion —E C H

RIPLEY H S, AND G N PAPANICOLAOU

The menstrual cycle with vaginal smear studies in schizophrenia: depression and elation. *Am J Psychiat* 98 567 1942

Observations were made on 817 menstrual bleedings of 221 patients suffering from schizophrenic and affective disorders. A more detailed study has been made in 31 cases by an analysis of the vaginal smears. A greater irregularity in menstrual interval than in a comparable normal group was found. A tendency to a delay, a weakened expression, or a temporary suppression of the follicular reaction was noted. Prolongation of the menstrual interval or amenorrhea was frequent. Short cycles also were observed. All these abnormalities are interpreted as the result of an adverse effect upon the growth of the ovarian follicles. A correlation between the severity of the illness and the degree of abnormality of the menstrual cycle was found. An improvement in the mental condition was usually accompanied by a change to a more normal menstrual function. The existence of an etiological relationship could not be ascertained —Author's abstract

ROSS, R A, E C HAMBLIN, W K CUYLER AND M BAPTIST

Evaluation of colorimetric quantitation of 17 ketosteroids. Application to gynecology. *Am J Obst & Gynec* 42 607 1941

A summary of the data secured from the quantitation

of 5,700 24 hour specimens of urine of 216 women for 17 ketosteroids is reported. Theories in regard to adrenal hyperactivity sequential to intercurrent estrogenic failure and to climacteric ovarian failure are advanced. Practical diagnostic and prognostic data may be secured by these quantitations in some virilizing syndromes and in severe intercurrent estrogenic failure —E C H

RUDOLPH, G DE M

The experimental effect of sex hormone therapy upon anxiety in homosexual types. *Brit J M Psychol* 18 317 1941

Chorionic gonadotropin (antuitrin S) was administered to 4 homosexual patients, 2 men and 2 women, suffering from anxiety. One was given testosterone propionate (testoviron) later. All the patients had had varying periods of psychotherapy, with small success. Marked improvement of the anxiety occurred during the administration of 6 to 13 injections of chorionic gonadotropin over varying lengths of time. A similar result occurred in 1 man who was given two courses of testosterone propionate, of 7 doses each. There was some change in those secondary sex characteristics which had shown some abnormality. The anxiety returned at periods of from a few days to four months after the cessation of treatment. The author concludes on the basis of this experience that anxiety in predominantly homosexual patients may be directly dependent on deficiency of "sex hormone." —Abst, *Arch Neurol & Psychiat* 46 1090 1941

SALMON, U J, R I WALTER AND S H GEIST

The use of estrogens in the treatment of dysuria and incontinence in postmenopausal women. *Am J Obst & Gynec* 42 845 1941

Sixteen postmenopausal women with frequency, urgency and incontinence were treated intramuscularly with estrogens. All but 3 were relieved of symptoms. It is suggested that estrogenic therapy be tried in postmenopausal women prior to vaginoplasty or urethroplasty for urinary symptoms —E C H

SCHOENECK, F J

Gonadotrophic hormone concentration in emesis gravidarum. *Am J Obst & Gynec* 43 308 1942

Studies, based upon the use of a quantitative Friedman test, are reported upon 173 patients distributed as follows: 72 patients without nausea and vomiting, 62 patients with 'physiologic' vomiting, 24 patients with 'excessive nausea and vomiting', and 15 patients with 'pernicious' vomiting. The data obtained indicate that increased urinary gonadotropin values are associated with nausea and vomiting of pregnancy —E C H

SOULE, S D

Anhydro hydroxy progesterone in threatened interruptions of pregnancy. *Am J Obst & Gynec* 42 1009 1941

Twenty patients were treated with anhydro hydroxyprogesterone and progesterone, only 4 miscarried. It is concluded that anhydro hydroxy progesterone is a valuable medication under these circumstances —E C H

STILES, M. H.

Basal metabolic rate in low grade chronic illness. A statistical analysis of 166 cases. *Am. J. Clin. Path.* 11: 871. 1941.

One hundred sixty-six individuals with low grade chronic illness had a mean B.M.R. of  $-8$ . The mean B.M.R. was lower in males than in females, although the difference was insignificant. Individuals below the age of 20 showed a more marked decrease of B.M.R. Patients with moderately severe or severe symptoms showed significantly lower rates than those with mild symptoms.—E.V.H.

WEISMAN, A. I., A. F. SYNDER AND C. W. COATES.

The 'Frog' test (*Xenopus laevis*) as a rapid diagnostic test for pregnancy. *Am. J. Obst. & Gynec.* 43: 135. 1942.

Diagnoses in 53 tests using the South African clawed frog were 100% correct. Technic for the test is described.—E.C.H.

## ADRENALS

HARTMAN, F. A.

The adrenal hormones in medical practice. *J. Am. Med. Assoc.* 117: 1405. 1941.

The adrenal cortical hormone is discussed under the following headings: electrolyte metabolism, general metabolism, carbohydrate metabolism, and the relationship to vitamins, pigmentation, lactation, and the central nervous system. The treatment of Addison's disease is outlined in detail.—C.P.

PATTERSON, J., I. M. MCPHEE AND A. W. GREENWOOD.

17-Ketosteroid excretion in adrenal virilism. *Brit. M. J.* 1: 35. 1942.

By the modification employed, the 17-ketosteroid excretion expressed as milligrams of androsterone per 24 hours were found to be as follows: 12 normal women 3.5 to 14.6, average 7.4; 9 normal men 9.4 to 20.9, average 13.3. There was a positive correlation with body weight in both men and women, but no change was observed with the menstrual cycle in 15 determinations on one individual. The values were distinctly elevated in 4 cases of adrenal cortical tumors (27-270), and in 7 cases of adrenal hyperplasia (primary or prepubertal virilism) (34-64), but not in 21 cases of secondary or post-pubertal virilism (9.0-33.4). No distinct changes in 17-ketosteroid excretion were noted in 3 feminized males, nor in hypogonadism, homosexuality, and hypopituitarism. The cases classified by the authors as secondary virilism exhibited hirsutism with or without menstrual disturbances but no mention is made of other signs of masculinization, e.g., enlargement of the clitoris. Consequently these cases are probably ones which are usually classified under the heading 'hirsutism without true masculinization' and thus the low values found in this group assume diagnostic importance.—E.B.A.

WILSON, D. M., F. J. ROBINSON, M. H. POWER, AND R. M. WILDER.

Diagnosis of Addison's disease. Further experience

with the Cutler-Power-Wilder sodium chloride restriction test. *Arch. Int. Med.* 69: 460, 1942.

The results of examination of 63 patients by means of a 52 hour salt restriction procedure are reported. Of 16 patients with Addison's disease, symptoms of crisis which necessitated discontinuance of the test developed in 10; 5 patients responded with the typically high concentrations of chloride and sodium in the final 4 hour specimen of urine, while 1 patient who responded atypically had concentrations of sodium and chloride in the plasma sufficiently low to be diagnostically significant. With 1 exception 44 patients not having Addison's disease responded with typically low concentrations of sodium and chloride in the final 4 hour specimen of urine. In the exception noted normal concentrations of sodium and chloride in the plasma and the failure of the patient to react unfavorably to a prolongation of salt restriction aided in the exclusion of the diagnosis of Addison's disease. Three patients who had Addison's disease treated with desoxycorticosterone acetate through the test procedure responded similarly to that of subjects who did not have Addison's disease. The test subjects the patient who has Addison's disease to some danger. Its chief value lies in the diagnosis of or exclusion of adrenocortical insufficiency when uncertainty exists. The clinician who subjects a patient to this test should be prepared to recognize and treat acute adrenal cortical insufficiency should it occur.—I.B.

## GONADS

BICKERS, W.

Uterine contractions in dysmenorrhea. *Am. J. Obst. & Gynec.* 42: 1023. 1941.

Uterine contractions in 15 women, aged 16 to 26 years, with severe dysmenorrhea were studied by the intra-uterine balloon method and recorded kymographically. High amplitude contractions characterized dysmenorrhea. Progesterone and testosterone did not alter these contractions; the administration of estrogens during the early part of the cycle reduced contractions and pain.—E.C.H.

EDITORIAL.

Climacteric in aging men. *J. Am. Med. Assoc.* 118: 456. 1942.

This editorial reviews the evidence for a climacteric in the male. Arguing by analogy with the female sex cycle and with the knowledge of the effects of castration in the male, no definite data for such a climacteric are available.—C.P.

FARROW, J. H., AND HELEN Q. WOODARD.

The influence of androgenic and estrogenic substances on the serum calcium. *J. Am. Med. Assoc.* 118: 339. 1942.

Testosterone propionate therapy was given to 33 female patients with breast cancer metastases to bone. Unlike castration of these patients, the testosterone accelerated the growth of the metastases. The serum Ca was elevated (perhaps indirectly) by the therapy.—C.P.

## GEIST, S H, J A GAINES AND U J SALMON

The effect of gonadotropins upon the human ovary  
*Am J Obst & Gynec* 42 619 1941

The ovaries of 91 women aged 25 to 50 years (52 of whom were past 40 years of age), were studied at operations following varying dosage schedules of the following gonadotropins or combinations of them: pituitary, chorionic, equine, chorionic and pituitary, chorionic and equine, and chorionic and diethylstilbestrol. In no instance could the occurrence of ovulation be related to the therapy.—E C H

## GEIST, S H, AND U J SALMON

Androgen therapy in gynecology *J Am Med Assoc*  
117 2207 1941

Therapeutic effectiveness of androgens in the female stems from their ability a), to nullify or modify the action of estrogens, b), to suppress or decrease the production of estrogens by the ovary, c), to inhibit the proliferative processes in the endometrium, d), to inhibit the reactivity of the uterine musculature, and e), to inhibit the gonadotropic activity of the hypophysis.—C P

## GREENBLATT, R B

Histologic changes in the ovary following gonadotropin administration *Am J Obst & Gynec* 42 983 1941

Thirty six women, aged 15 to 49 years, were treated preoperatively with diverse gonadotropins and their ovaries subsequently were studied at operation. The production of corpora lutea was more common following the use of a mixture of pituitary "synergist" and chorionic gonadotropin. Regardless of what gonadotropin was used follicular atresia was the most commonly encountered finding.—E C H

## HAMBLEN, E C

Uses and limitations of estrogens in gynecic practice  
*J Am Med Assoc* 117 2205 1941

Practical estrogen therapy is discussed under the following headings: therapy of ovarian failure, therapy of local hypoplasias, estrogenic therapy to depress other glands, local vaginal effects, and empiric uses.—C P

## HENDERSON, D N

Granulosa and theca cell tumors of the ovary *Am J Obst & Gynec* 43 194 1942

The clinical records and pathologic findings of 30 patients with ovarian tumors of granulosa or theca cell type are reported.—E C H

## JOHNSTON, J A

Factors influencing retention of nitrogen and calcium in period of growth IV Effect of estrogen *Am J Dis Child* 62 708 1941

The report deals with continuous balance studies on N and Ca and determination of the B M R. on 6 girls at puberty. Estrone was administered to 5 in doses varying from 12 000 to 36 000 u and diethylstilbestrol to one. A depression of the Ca balance in both the urinary and fecal fractions was obtained in 5 and an additional N depression in 3 with the estrone. Diethylstilbestrol likewise resulted in a diminution of both Ca and N.—M B G

## KENNY, M, AND D DALEY

Experience with the intravenous use of the follicle-stimulating hormone of the anterior pituitary in menstrual disorders *Proc Roy Soc Med* 34 804 1941

The authors used a preparation of pregnant mare's serum intravenously in 3 types of menstrual disorders (1) Metropathia hemorrhagica. In 3 of 4 cases regular menstruation was induced. Doses of 500 units were given intravenously on 3 successive days. In 2 of these cases ovulation was produced as judged by the finding of secretory endometrium at the succeeding menstrual period. (2) Menorrhagia with ovulation. Very doubtful results were obtained in 2 cases of this type. (3) Secondary amenorrhea. One of 3 cases seemed to respond but biopsy confirmation of ovulation was not possible.—J E H

## MARWIL, T B, AND D C BEAVER

Brenner tumor of the ovary associated with uterine bleeding *Am J Obst & Gynec* 43 99 1942

A Brenner ovarian tumor in a woman 77 years of age was associated with vaginal bleeding and a slightly hyperplastic estrogenic endometrium.—E C H

## NOVAK, E, AND E H RICHARSON, JR

Proliferative changes in the senile endometrium *Am J Obst & Gynec* 42 564 1941

One hundred and thirty-seven endometria from women 2 to 40 years past menopause were studied. Less than one half of these was atrophic. Forty-two showed proliferative activity, moderate in 14, marked in 28. It is suggested that the adrenals are the source of the post-menopausal estrogen operative in these cases.—E C H

## SALMON, U J, S H GEIST AND R I WALTER

Treatment of the menopause *J Am Med Assoc*  
117 1843 1941

Implantation with loose crystals and compressed pellets of  $\alpha$  estradiol,  $\alpha$  estradiol benzoate, and  $\alpha$  estradiol dipropionate was carried out on a series of 180 patients. A control series of 18 menopausal patients was given a single injection of comparable amounts of estrogen in solution in oil. The implantation of estrogens in the form of loose crystals or compressed pellets was more efficient than the injection of comparable amounts of hormone in oil. Loose crystals of  $\alpha$  estradiol and  $\alpha$  estradiol benzoate were more effective than the compressed pellets of the same chemical constitution. The longest period of symptomatic relief was obtained by the implantation of  $\alpha$  estradiol crystals.—C P

## SCHAUFFLER, G C

Double uterus with pregnancy *J Am Med Assoc*  
117 1516 1941

The author's experience with 11 cases of double uterus is reviewed through 32 pregnancies. Symptoms may be irregular menstruation, dyspareunia, repeated abortion, or malposition of the fetus.—C P

## VEST, S A, AND B BARELARE, JR

Peroral use of methyl testosterone *J Am Med Assoc* 117 1421 1941

Methyl testosterone per os was effective in 2 patients

(a eunuchoid and a castrate) treated over periods of 17 to 20 months. The optimal dosage was 20 to 30 mg. daily. No evidence of toxicity was noted. Previous removal of the stomach of one patient did not affect the therapeutic results.—C.P.

## HYPOPHYSIS

NIEUWENHUIZEN, C. L. C. van.

Absorption of carbohydrate, fat and vitamins in hypophyseal insufficiency. *Acta med. Scandinav.* 108: 194. 1941.

Studies were made of the absorption of carbohydrate fat and vitamins in 4 patients with hypophyseal disease. In a case of acromegaly and in one with diabetes insipidus there was marked deficiency in absorption of vitamins A and B<sub>1</sub>, fat and carbohydrate with symptoms of non-tropical sprue which were relieved by administration of desoxycortin. A case of Cushing's disease and a case of adiposa progenitalis associated with diabetes insipidus showed no disturbance in absorption. The author suggests that non-tropical sprue may be the result of a disturbance in the hypophysis or diencephalon.—F. R. Vanzant (*courtesy Biol. Abstracts*).

ROWLANDS, R. A., AND S. L. SIMPSON, with a Pathological Report by DOROTHY S. RUSSELL, AND H. M. TURNBULL.

The skeletal and other changes found in a case of suprasellar cyst of Rathke's pouch. *Brit. J. Surg.* 29: 115. 1942.

An interesting example of Simmonds's cachexia in a male of 43, with a suprasellar pituitary cyst, is described.

The patient's general appearance was that of an emaciated wizened dwarf, with a progeric countenance. He ceased to grow at the age of 12, and never developed any secondary sexual characteristics. His genitals were minute, and his bony epiphyses ununited. Intellectual processes and general knowledge were of good adult standard. Narcolepsy and catalepsy were interesting complications, probably of hypothalamic origin. Diabetes insipidus was also a feature. The basal metabolism was  $-52\%$ , and the temperature always subnormal, with great sensitivity to cold. The suprasellar cyst was indicated by bilateral optic atrophy and a radiogram of the skull. The patient died in coma, without operative interference.—S.L.S.

## PANCREAS

ZUBIRAN, SALVADOR.

Functional diabetes. *Prensa méd. mex.* 60: 113. 1941.

Functional diabetes occurs in middle life, especially in obese persons. It is distinguishable from true diabetes by a normal glucose oxidation as can be demonstrated by calorimetric tests. The hyperglycemia is caused by deficient ability of the liver to fix glucose as glycogen. The disturbance is caused by infiltration of the liver with fat, and is curable. All obese persons show a tendency toward an elevated glucose curve and are potential diabetics.—A. E. Meyer (*courtesy Biol. Abstracts*).

## THYROID

ABRAMSON, D. I. AND S. M. FIERST.

Resting peripheral blood flow in the hyperthyroid state. *Arch. Int. Med.* 69: 409. 1942.

The rate of blood flow through the hand, forearm and leg was studied in a series of 12 hyperthyroid subjects by means of the venous occlusion plethysmographic method. In 7 of the patients the changes in flow for some time after thyroidectomy were observed. The average resting blood flow in the forearm and leg of the hyperthyroid subjects was significantly increased over that of a control series. After thyroidectomy there was a decrease, with a return to a normal level in 11 to 63 days after operation. The average resting blood flow in the hand was not strikingly increased, although some of the individual readings were significantly greater than those of the control group. After thyroidectomy in the majority of cases the flow decreased to a subnormal level. The rate of fall in peripheral blood flow to normal levels, subsequent to operation, occurred more slowly than did the decrease in pulse rate and pulse pressure.—I.B.

ANDERSON, A. B.

Hyperthyroidism: Relation of the basal metabolism to the clinical signs. *Brit. M. J.* 2: 117. 1941.

A correlation of the basal metabolic rates in 230 cases with 6 cardinal clinical signs of hyperthyroidism, i.e. thyroid enlargement, exophthalmos, tremor, tachycardia, sweating and loss of weight, showed that 71 of 72 cases exhibiting enlargement of the thyroid, exophthalmos and at least one of the other signs had elevated B.M.R.'s (higher than plus 15%). Likewise 30 of 31 cases with all the signs except exophthalmos exhibited increased B.M.R.'s. The metabolic rates were high in only a small percentage of patients with fewer than 4 of the above signs.—E.B.A.

COLVIN, E. D., R. A. BARTHOLOMEW AND W. H. GRIMES.

A comparison of thyroid extract and iodine therapy in the prevention of toxemia of pregnancy. *Am. J. Obst. & Gynec.* 43: 183. 1942.

Data secured upon a group of obstetrical patients treated during pregnancy with thyroid substance in daily doses ranging from 1.5 to 3 grains and upon a similar group treated with an iodine preparation in daily doses equivalent to 1.8 gr. of iodine are reported. 171 patients with 'mild vascular disease' were studied: 10 (10.3%) of 97 control patients, 5 (14.3%) of 35 thyroid treated patients and 2 (5.1%) of 39 iodine treated patients developed toxemia. 589 'normal' patients were studied: 75 (23.1%) of 316 control patients, 23 (27%) of 85 thyroid treated patients and 12 (6.4%) of 188 iodine treated patients developed toxemia. 349 patients with 'moderate and severe toxemia' were studied: 13 (8.1%) of 161 'nontreated' patients and 6 (3.2%) of 188 iodine treated patients continued to have severe toxemia.—E.C.H.

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## Testosterone Therapy of Male Eunuchoids

### III. Sublingual Administration of Testosterone Compounds

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AS STATED in the first paper of this series (1) entitled, 'Implantation of testosterone compounds in cases of male eunuchoidism', "the effectiveness of an endocrine preparation is measured best by its capacity to restore normal function in a characteristic endocrinopathy caused by its deficiency. Eunuchoidism, or male hypogonadism, is the clinical state in which the primary deficiency resides in the testes, and therefore it represents an ideal clinical condition for testing the effectiveness of an androgenic substance."

The clinical efficacy of parenteral administration of testosterone propionate in the treatment of male eunuchoidism and of adult forms of male hypogonadism has been confirmed abundantly. For the past 4 or 5 years this testosterone preparation in oil has been available commercially. The effectiveness of implanting pellets of crystalline testosterone compounds, principally methyl testosterone, has been reported (1). It was demonstrated that in some respects the continuous absorption from such pellets was more efficient and presumably more economical than the injection of the hormone in oil, since only approximately one fifth of the dose was required to obtain similar results. Furthermore, the improvement achieved by such implants was maintained for about 7 weeks,

while 2 to 7 injections per week were required to accomplish the same results by the parenteral method.

In the second paper of this series (2) entitled, 'Clinical comparison of parenteral, implantation, and oral administration of testosterone compounds in male eunuchoidism,' the effects produced in 3 cases by single massive implants of 600 to 800 mg. were reported. Formerly 16 to 23 tiny pellets had been introduced through a large bore needle in doses aggregating from 83 to 195 mg. In the modified procedure a 1-inch incision was necessary and pellets of 200 mg each were implanted. Contrary to expectations, the active stimulation was not prolonged in direct ratio to the size of the dose. The pellets ceased to be effective much sooner than was anticipated. In 2 of the 3 cases, one-fourth to one half of the original implant was recovered subsequently. It had evidently been rendered non-absorbable by formation of a connective tissue capsule. Large implants, therefore, were disappointing with regard to both duration of effect and wastage of material. Furthermore, massive implants necessitated a minor surgical operation which did not seem warranted by the additional benefits received.

Methyl testosterone by mouth was surprisingly effective in maintaining the improved status previously attained by the parenteral or implantation methods. Indeed, the response was augmented both subjectively and objectively. The dose required in 6

cases was 2 to 4 times the intramuscular dose. This mode of therapy was found to be the simplest, most convenient and possibly the most economical. In cases of severe eunuchoidism in adults, the initial oral dose required was between 50 and 100 mg. daily. Maintenance doses as a rule were between 10 and 30 mg. daily. Oral therapy alone produced gain in weight, elevation of the basal metabolic rate, growth of the external genitalia and prostate, more vigorous growth of sexual hair, deepening of the voice, increased libido and frequency of erections, as well as increased strength, endurance and mental and emotional animation.

In a subsequent paper (3) the clinical indications for testosterone and the various modes of administration were reviewed. Preliminary mention was made of the sublingual absorption of testosterone compounds. The purpose of the present paper is to report our clinical experiences with this method in 9 cases.

Anderson, Haymaker and Henderson (4) in 1940 reported that desoxycorticosterone dissolved in propylene glycol was equally effective, dose for dose, when it was absorbed from under the tongue as when it was administered parenterally. This discovery obviated the necessity for daily injections in patients suffering from Addison's disease (desoxycorticosterone is ineffective when swallowed). Admittedly, the same advantage does not apply to testosterone because of the remarkable oral potency of methyl testosterone. Nevertheless, we are able to report that the methyl and propionic esters of testosterone and above all pure testosterone are successfully absorbed sublingually.<sup>1</sup>

The solution of each of these three substances contained 25 mg. of hormone per cc. The dropper used for its administration was calibrated in 0.1 cc. divisions. The maximum amount that could be taken comfortably at one time was 0.2 cc. (which contains 5 mg. of hormone). The patient was instructed to measure the dose in the dropper, to tilt back the head and to place the measured dose under the tongue. He was instructed to hold this position, with the mouth open, until the substance was apparently absorbed, for which 2 to 5 minutes usually were required. During this time he was asked not to swallow. This procedure was repeated 2 to 5 times daily, depending on the dose required, namely 10 to 25 mg. We believe that patients probably would object to going through this performance more than 5 times a day.

While the case records for this paper were being compiled, Joel of Basle University (5), in 1942, reported that he administered testosterone sublingually in "especially hard-pressed tablets" which he con-

sidered a more convenient and pleasant-tasting vehicle than the propylene glycol solution. Each tablet contained 5 mg. of methyl testosterone. He treated 19 females, 15 of whom were suffering from climacteric disorders, 2 from dysmenorrhea and 2 from mastodynia. The dose varied from 1 tablet daily in mild cases (5 mg.) to 6 tablets daily in severe cases. The results were gratifying in most instances. Furthermore, Salmon and Geist (6) as well as Hall (7) have shown that sublingual administration of  $\alpha$ -estradiol in propylene glycol produces a typical cornification in the vaginal smear.

Our observations with respect to sublingual administration of testosterone are confined to the male. Five of the 9 cases included in this series have been reported in previous papers (1, 2) in more elaborate detail. The patients in these 5 cases were characteristic examples of severe eunuchoidism which originated prior to normal adolescence and were exceedingly immature at the ages of 21, 24, 24, 24 and 31 years, respectively. Subsequently they had been treated either with testosterone propionate administered parenterally or with methyl testosterone administered in pellet form by implantation or in tablet form orally. They all had been vastly improved and successfully maintained by means of one or more of these procedures. Since they had been observed for a sufficiently long period of time to permit critical comparative appraisal of parenteral, implantation and oral administration of testosterone compounds, we considered them as excellent controls for a trial of the sublingual method of administration. The remaining 4 patients in this series represent several types of male hypogonadism. None of them had received any form of testosterone therapy before. All of them displayed improvement after sublingual therapy. No other treatment was given. We therefore believe that the benefits achieved may be ascribed to the sublingual administration of testosterone.

#### CASE REPORTS

*Case 1; R.C., (U 57397). Case 7 in (1); Case 1 in (2)* with photographs. The patient was 24 years old when he was first seen in April, 1940, with characteristic pre-adolescent eunuchoidism. His height was 66.75 in. and his weight, 120 lb. He had typical disproportionately long extremities, shaved infrequently and had a high-pitched voice. The pubic hair was scant and axillary growth was moderate. The penis was small (length 5 cm.) and the testes were the size of small olive pits. The left testis was undescended. The prostate was barely palpable. The bone age was 16 to 17 (at 24 years of age).

Implants of methyl testosterone were begun on April 17, 1940. During the following 8 months 4 implants of tiny pellets were introduced subcutaneously through a large-bore needle; the dose varied from 143 to 180 mg. Marked subjective and objective improvement resulted.

<sup>1</sup> These preparations were supplied by The Schering Corporation, Bloomfield, N. J.

Priapism persisted for one week following the first implant. The stimulating effects lasted from 4 1/2 to 7 weeks after each implantation during which time the patient had frequent erections and some nocturnal emissions, he masturbated occasionally. The length of the penis had increased to 8 cm, its circumference was 8 cm. Scrotum and testes had increased in size, the left testis had descended shortly after the first implant. The patient had gained 13 lb and felt stronger. His voice had deepened, the body hair had increased and he shaved every week.

In December, 1940, 4 pellets of methyl testosterone totalling 800 mg. were implanted through a small incision in the back. The patient noticed unmistakable effects within a few days. During the first week he had 3 to 4 erections daily and 2 nocturnal emissions. The voice deepened somewhat, the beard became heavier and the penis increased 75 cm in length. Two months later the muscles of the arms and legs had developed noticeably and his general strength had improved. He reported 5 to 6 erections daily, 3 nocturnal emissions a week and greater attraction toward the opposite sex. The size of the genitalia was unaltered. He had gained 3 1/2 lb, the total gain in weight under implantation therapy was 16 1/2 lb. He had not received any other treatment, so that this gain was directly attributable to the implantations of male hormone.

In April 1941, 5 months after the last implant, the effects had definitely 'run out'. Only partial erections occurred every 1 to 2 days and nocturnal emissions had decreased. However, the size of the genitalia had not changed, the prostate was about two thirds normal size. The bone age was still 17 years. The patient complained of sensitivity at the site of the implant. A local area of redness and fluctuation was opened surgically and a small cavity containing necrotic and purulent material was encountered just beneath the skin. The entire area of the implant was dissected out by cautery. The tissue contained 4 pellets of testosterone which after drying weighed a total of 370 mg. Each pellet was surrounded by a yellowish capsule of fibrous tissue and a foreign body and phagocytic reaction. Apparently this reaction had rendered nearly one half of the 800-mg. implant ineffectual.

During a short interim of 4 weeks the patient received tablets of methyl testosterone orally in doses of 10 mg. three times daily. He felt well and gained 9 lb, to a weight level of 155 lb. Erections increased to 3 to 4 daily, each week the patient masturbated once and had nocturnal emissions twice. On May 15, 1941, sublingual administration of methyl testosterone in propylene glycol in doses of 5 mg. twice daily was begun. After 3 weeks the dose was increased to 5 mg. three times daily, and after the fourth week to 5 mg. four times daily. The patient reported that the results did not equal those obtained with the tablets. Erections decreased to two daily and nocturnal emissions ceased for 6 weeks, although the patient continued to masturbate about once a week. After 2 months the medication was changed to testosterone propionate in propylene glycol given sublingually in doses of 5 mg. four times daily. The effects after 2 1/2 months were similar to those brought about by the methyl testosterone. Erections occurred once or twice daily but only 2 nocturnal emissions occurred in that period of time. On Oct. 23, 1941, sub-

lingual treatment with free testosterone in propylene glycol in doses of 5 mg. four times daily was instituted. As a result the erections increased to 2 to 3 daily, but they were not as satisfactory as those which had resulted from the oral dose.

At the time of this report the patient has been receiving testosterone sublingually for 5 months. The frequency of erections has gradually decreased to 1 every 3 to 4 days. He has continued to masturbate every 7 to 10 days, but the amount of secretion has lessened. The size of the external genitalia is unaltered. The patient has lost weight and has become somewhat depressed. He believes that he has lost some of the firmness of his general musculature and that his voice has become slightly higher in pitch. He has continued to shave once every 3 weeks. A survey of the 10 months of sublingual therapy shows that the patient apparently has lost ground in the subjective and functional sphere. The only objective change is loss of weight from 155 to 141 1/2 lb. However, 7 pounds of this loss occurred during one week under circumstances surrounding his marriage which he decided to consummate in spite of the regression of his condition. When he was last seen one week after his marriage, he had not achieved a satisfactory penetration.

**Case 2 L K (U 2063.4)** Case 3 in (1), Case 3 in (2) with photographs. The patient was 24 years old when he was first seen in September, 1937. He had been operated upon for bilateral cryptorchidism at the age of 16, at that time the left testicle had been atrophic. The height was 71 7/8 in., his weight, 146 lb. He had the disproportionately long arms and legs of a typical eunuchoid. He had never shaved and his voice was high pitched. Pubic hair was sparse and only a very few axillary hairs were present. The penis was small (length 4 7/8 cm.) and the scrotal content consisted of some questionable tissue in the left side. The bone age was 15 (at 24 years of age). Equine gonadotropic hormone had been administered (48 injections in 4 months) without benefit.

Testosterone propionate was given parenterally for 16 months, the total amount was 3500 mg. Thereupon the patient's voice deepened and he had occasional nocturnal emissions and practiced masturbation. The hair in the pubic escutcheon increased moderately and the axillary hair grew considerably. The length of the penis was 8 cm (formerly 4 7/8 cm.) and the circumference was 10 cm. The testes were palpable, the right was bean sized and the left was the size of a small olive. The bone age was 19 years (an acceleration of 4 years in 2 years' elapsed time). Increased mental and emotional responses as well as vigor and strength were evident. He had gained 20 lb.

In the following year (November, 1939 to November, 1940) the patient received 5 implants of methyl testosterone introduced subcutaneously through a large bore needle. The dosage, given in tiny pellets, varied from 101.3 mg. to 164 mg. The improvement obtained by the parenteral method was maintained both subjectively and objectively. Libido remained unchanged for as long as nine weeks. During this period the patient married and was able to have successful intercourse as often as once a week. The length of the penis increased further, 2 cm., and the patient now shaved once a week.



In November, 1940, when the patient was 27 years old, oral therapy was instituted. For the first 4 months he received one 10-mg. tablet of methyl testosterone 3 times daily. The effect of the implant given 2 months before had begun to wane so that he had not had intercourse during the month prior to institution of oral therapy. The tablets stimulated him almost immediately; 2 days later he had erections three times a day and reported successful intercourse three times in the subsequent month. Four months after the beginning of oral therapy, the dose was reduced from 30 to 20 mg. daily to determine whether this diminished amount would suffice. A month later the patient reported that within 2 weeks of reducing the dose the frequency of erections had diminished somewhat. However, libido had remained the same. It seemed doubtful that a dose of 20 mg. daily by mouth would continue to be adequate for this patient. It was therefore again increased to 30 mg. daily. Evidently oral administration of 210 mg. a week had, in this patient, an effect equivalent to parenteral administration of 75 mg. a week. This is a ratio of not quite 3 to 1.

In May, 1941, the treatment was changed to sublingual administration of methyl testosterone in propylene glycol in doses of 5 mg. twice daily. During the subsequent 3 months the frequency of erections diminished to 3 to 4 weekly but the patient was still able to have satisfactory intercourse once each week and in general continued to feel well. The size of the genitalia did not change and the weight remained stationary. Medication was shifted to sublingual administration of testosterone propionate in propylene glycol in doses of 5 mg. twice a day and was continued on this basis for 2 months. No noticeable changes in effect occurred. On Oct. 20, 1941, therapy was changed to sublingual administration of free testosterone in propylene glycol in doses of 5 mg. twice daily. Thereupon the patient reported slight improvement of libido and general strength. Erections occurred two to three times per week. Three months later the dose was increased to 15 mg. daily.

At the time of this report the patient has received the same preparation for 5 months. He has daily erections and continues to have satisfactory intercourse every week. The genitalia have not altered in size. Since sublingual therapy was begun he has complained of sensitivity of the nipples. A small amount of glandular tissue was felt under each nipple and for a short time small amounts of fluid could be expressed. It appears that in this typical eunuchoid a dose of 15 mg. of testosterone a day sublingually is able to maintain the improved status for which 30 mg. of methyl testosterone taken orally were required. In this patient, therefore, therapy by the sublingual route appears to be more economical than by the peroral route.

*Case 3; B.C., (U 4545). Case 6 in (1) with photographs; Case 5 in (2).* The patient was 17 years old when he was first seen in March, 1933. He showed characteristic evidence of preadolescent eunuchoidism with disproportionately long extremities. The height was 63.75 in. and weight 114 lb. The voice was high-pitched and he had no beard nor axillary or pubic hair. The penis was small (7 cm. in length) and the testes were the size of small olives. The prostate was barely palpable. The bone age

was 15 to 17 years (at 17 years). The B.M.R. was -2 per cent. Treatment with chorionic gonadotropin, thyroid substance and androstine had had negligible effect.

In November, 1936, when the patient was 21 years of age, treatment with testosterone propionate was begun. At first 5 mg. and later 25 mg. were given 3 times each week parenterally. This plan was continued for a period of 3 years, until November, 1939. The total dose was 10,250 mg. Marked changes occurred during this time. The patient matured markedly, shaved every 2 weeks, had moderate growth of axillary and pubic hair, and the penis had adult dimensions. Treatment then had to be discontinued for 4 months with consequent subjective and objective regression of noticeable degree. The penis shrank 2 cm. in length.

In March, 1940, implantation therapy was instituted. During the following 8 months the patient received 3 implants varying in dosage from 109.6 to 138.3 gm. Sexual stimulation and an increase in general strength returned. The patient's weight remained constant, but the penis again increased in length, from 9.25 to 12 cm.

Oral therapy was begun in November, 1940, with 10 mg. of methyl testosterone 3 times daily. This resulted in such marked sexual stimulation that on Dec. 19, 1940, the dose was reduced to 10 mg. twice daily and in February to 10 mg. daily. Two months later the patient expressed his entire satisfaction with the effects of this dose. His general strength had improved and he had gained 10 lb. during the period of oral treatment. He shaved once twice a week. Erections occurred one to two times daily. He masturbated twice a week and experienced an occasional nocturnal emission. The external genitalia were slightly larger and of full adult size. In contrast, the penis state remained small and soft, about one-fourth normal size. The patient stated that he preferred oral to parenteral treatment, principally because it was more convenient. He also preferred oral therapy to implantations because the tablets provided a more uniform stimulus whereas the implants 'built up to a peak and then let down.'

In April, 1941, sublingual treatment with methyl testosterone in propylene glycol in doses of 5 mg. twice daily was begun. After 2 months the patient reported that the effect was comparable to that of one 10-mg. tablet of methyl testosterone taken daily by mouth. Erections occurred at first twice daily and later once daily. Each week the patient masturbated about twice and had one nocturnal emission. In June, 1941, the therapy was changed to testosterone propionate administered sublingually in doses of 5 mg. twice daily, and was continued for 2 months with comparable effect. Thereupon free testosterone in propylene glycol was administered sublingually in doses of 5 mg. twice daily. More stimulation resulted and several erections occurred every night. After 6 months the patient reported erections twice daily and emissions twice weekly. The size of the genitalia had slightly decreased. The length of the penis was 12.25 cm. (formerly 13 cm.). During the 10 months of sublingual therapy he had lost 10 lb., 157.75 lb. however, this loss may in part be ascribed to change in occupation which required more strenuous physical exertion. He also complained of transient soreness and secretion from the nipples during sublingual therapy. In this patient a sublingual dose of 10 mg. dai

had an effect neither greater nor less than an oral dose of 10 mg

*Case 4, J J, (U 36521) Case 4 in (1) with photographs; Case 4 in (2)* The patient was 31 years old when he was first seen in May, 1938. He gave a history of epileptiform seizures from the age of 16, but he had had none in the preceding 2 years. He had typical preadolescent eunuchoidism with disproportionately long extremities. The height was 71 in., the weight 123 lb. The voice was high pitched, he had a few axillary hairs and a moderate amount of pubic hair. He clipped the fuzz from his face every 2 or 3 weeks. The penis was small (length 4.5 cm.). Testes and scrotum were very small, the prostate was not palpable. The bone age was 18 years (at 31 years of age). He had been given equine gonadotropic hormone for 3 months without effect.

Parenteral administration of testosterone propionate was begun in January, 1939, in doses of 25 mg. three times a week for 1 year, the total dose was 3800 mg. Marked subjective and objective improvement resulted. He had frequent erections and practiced occasional masturbation and sexual intercourse. Other effects were increased strength and a gain in weight of 14.5 lb. The penis grew 3.5 cm. so that it now measured 8 cm. in length. The prostate enlarged to one half normal size. The bone age advanced slightly.

In February, 1940, implantation therapy was instituted. During the succeeding 9 months the patient received 4 implants of methyl testosterone varying in size from 102.7 to 148.1 mg. The previous benefits were maintained and the stimulation from each implant lasted from 7 to 15 weeks. Libido and potentia remained about the same and the penis grew slightly larger, to 9 cm. in length.

In November, 1940, oral therapy of methyl testosterone 10 mg. three times daily, was begun. Sexual stimulation was prompt, it was noticeable in 48 hours. The patient had successful intercourse twice in the following 2 weeks and erections two and three times daily. The penis grew 1.75 cm. in length and 1.25 cm. in circumference in these 2 weeks. Five months later, on April 3, 1941, the patient had gained 5 lb. and had felt an increase in strength. The bone age had advanced to between 19 and 22 years of age. The subjective benefits previously obtained from parenteral and implantation therapy were well maintained on a dose of 30 mg. daily by mouth. No further significant change occurred in the size of the genitalia and the secondary sexual characteristics were about the same as when oral therapy was begun. The size of the prostate had not changed during the previous 8 months.

On April 14, 1941, sublingual therapy was instituted with methyl testosterone in propylene glycol in doses of 5 mg. twice daily. During 3.5 months the sexual stimulation was as before. The patient continued to have erections 2 to 3 times daily, he masturbated once or twice each week and had occasional successful intercourse. During this period the patient contemplated marriage, but the plans were cancelled when he had an epileptiform seizure at his fiancée's home the day before the projected wedding. On July 25, 1941, treatment was changed to testosterone propionate in propylene glycol administered sublingually in doses of 5 mg. twice daily. It was continued for 2 months. The effects remained about the same. On Sept.

18, 1941, therapy with free testosterone in propylene glycol in doses of 5 mg. twice a day given sublingually was begun. Sexual function continued unchanged. On Nov. 29, 1941, a specimen of spermatid fluid was obtained by masturbation. Microscopic examination did not reveal any young or mature spermatozoa. In December, 1941, the patient reported that he had occasional orgasms without emissions following masturbation. The erections had decreased to 1 or 2 a week and his condition was evidently regressing. In January, 1942, the dose was increased to 15 mg. daily. The following month he reported a slight increase in the number of erections. However, at his last visit in March, 1942, he reported only 1 to 3 erections weekly and no nocturnal or other emissions. The penis was slightly smaller than before, measuring 9 cm. in length, and he had lost 10 lb. during the 11 months of sublingual therapy. His general strength had not improved nor had hair-growth progressed. He still had occasional convulsive seizures. He expressed a preference for treatment by implantation, principally because of the greater duration of effect. In this patient, who was an example of severe eunuchoidism, a daily dose of 15 mg. of testosterone administered sublingually was far less effective than 30 mg. of methyl testosterone given orally.

*Case 5 F V, (U 62077) Case 6 in (2) with photographs* This 24-year-old sandblast helper was first seen as a private patient in July, 1940. His chief complaint was lack of sexual development which had been noted since he was 13 or 14 years old. Scant pubic hair had appeared at that time and the patient had masturbated occasionally, but with the ejaculation of only a very slight amount of secretion. Axillary hair appeared at the age 18, simultaneously with a moderate spurt in body growth. Since he was 21 years of age he had not masturbated but had had nocturnal emissions every 3 or 4 months with very scant secretion. He had had a few injections of testosterone propionate at weekly intervals which had caused some erections. He had never shaved.

The patient was 66.75 in. tall and weighed 155 lb. His extremities were disproportionately long. He looked younger than this stated age and the voice was high-pitched. He had scant axillary and pubic hair and no beard or other body hair. The blood pressure was 100 mm. Hg systolic and 60, diastolic. The penis was small, it measured 4 cm. from pubic bone to tip and 6.5 cm. in circumference. The testes were small and soft, the right measured 2.5 x 1.25 cm. and the left 1.5 x 1.5 cm. The prostate was about two-thirds normal size. Laboratory investigation revealed a relative lymphocytosis and a B M R. of -18 percent. Roentgenograms of the skull were normal. The bone age was 16 years (chronological age 24 years).

The patient was transferred to the University of California Hospital Clinic. On Aug. 8, 1940, he received an implant of 17 pellets of methyl testosterone, or a total of 117 mg. The effects were noticeable the next day and reached a peak of 4 to 5 erections daily 10 days later. A definite waning was noted after 5.5 weeks. In Sept. 19, 1940, a second implant was given which totalled 122.9 mg. in 14 pellets. The reaction was similar to that of the first implantation. The effect lasted 6 weeks. On Nov. 7, 1940, a third implant of 600 mg. of methyl testosterone

was placed in the subcutaneous tissues of the back. This large amount, consisting of 3 tablets of 200 mg. each, was given in order to determine whether augmented response would be obtained and whether such stimulation would be maintained for a much longer time. Two days after the implantation the patient began to have almost continuous partial priapism which lasted for a period of 7 to 10 days. The sexual stimulation gradually diminished and had subsided entirely by Jan. 24, 1941, approximately 11 weeks

therapy the penis had grown slightly longer, the testes were perhaps slightly larger and the voice had deepened. The prostate was considered of normal size. The blood pressure, which had been 100/60 mm. Hg. had risen to 120/70. Although he had had considerable libido, he had refrained from masturbating because someone had told him it was 'the wrong thing to do.' He volunteered a preference for oral over implant therapy because under the former he felt stronger and experienced more frequent erections.

Sublingual therapy was begun on June 12, 1941, with methyl testosterone in propylene glycol in doses of 5 gm. twice daily. The treatment was continued for 2 months during which time the number of erections gradually diminished to 2 a week. The patient masturbated once or twice a week and had occasional nocturnal emissions. Therapy was then changed to testosterone propionate in propylene glycol administered sublingually in doses of 5 mg. twice daily. During 2 months on this therapy no apparent change occurred. On Oct. 9, 1941, sublingual administration of free testosterone in doses of 5 mg. twice a day was begun. As a result the erections increased to 3 or 4 a week; the patient continued to masturbate about twice weekly. The treatment was continued with comparable results for 2 months. The dose then was increased to 5 mg. three times daily, but not much change in effect resulted. During the 8 months of sublingual therapy the patient's general strength had remained the same and he had gained 12 lb. to a weight level of 172 lb. The genitalia were not altered in size. He continued to shave every week. The pubic hair and the hair on his legs had increased somewhat. In this patient, another example of severe eunuchoidism, a daily dose of 15 mg. of testosterone given sublingually was fairly satisfactory although subjective sexual stimulation was not as pronounced as from 30 mg. daily of methyl testosterone given orally.

Case 6; F.R., (U 70152). When the patient was first seen on March 22, 1941, he was 16 years, 8 months old. His complaints were obesity and retarded sexual development. Pubic hair appeared at about the age of 15 years but the penis did not increase in size. The patient had never shaved. However, he had daily erections and masturbated occasionally.

The patient was 65.5 in. tall and weighed 170.25 lb. unclothed. He was rather obese about the abdomen and had full rounded thighs (fig. 1, A). He had no beard or axillary hair and very little pubic hair. No prostatic tissue could be palpated. The testes were of normal size. The penis measured 4 cm. in length and 6.5 cm. in circumference (fig. 1, C). The B.M.R. was -19 per cent. Plasma cholesterol was 119 mg. per cent. The bone age was 14 years (chronological age, 16 years, 8 months). The I.Q. was 90.

On April 7, 1941, sublingual administration of testosterone propionate in propylene glycol in doses of 10 mg. daily was initiated. By May 29, 1941, the pubic hair had slightly increased, but since this might have occurred naturally the dose was increased to 25 mg. daily. On July 10, 1941, the medication was changed to methyl testosterone in propylene glycol administered sublingually in doses of 25 mg. daily. During 6.5 months of sublingual

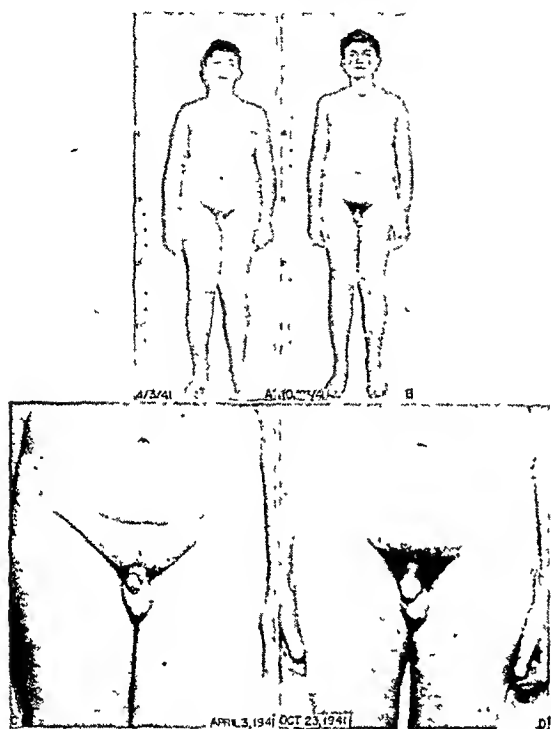


FIG. 1. Case 6, F. R. (U 70152): age 16 yr. 8 mo.; delayed maturity; treatment with testosterone administered sublingually. In the course of 7 months of treatment there was a growth of 2 inches in height and a loss of 10 lb. in weight, without restriction of diet. Note more masculine configuration, growth of penis and increased amount of pubic hair.

-after the implantation. The patient remarked that it had definitely 'run out.' The length of the penis was 5.75 cm. (an increase of 1.75 cm.); circumference was 8.25 cm. The right testis remained the same whereas the left had enlarged from 1.5 × 1.5 to 3 × 1.5 cm. Other effects noted were occasional nocturnal emissions, increase in general strength and more vigorous growth of beard and body hair. It is interesting to note that on implantation therapy alone the B.M.R. had risen from -18 to -2 per cent.

In order to compare the effects of small and large implants with oral administration, oral therapy was begun on Feb. 6, 1941, with a dose of 30 mg. daily. Within the first 48 hours the patient experienced frequent erections which occurred daily. Four nocturnal emissions occurred within the first 3 weeks and the relaxed penis had increased 1 cm. in length. The patient had gained 3 lb.

This patient had gained 9 lb. in 2 months on oral testosterone therapy alone. During 8 months of male hormone treatment, he had gained 20 lb. and had grown 1.5 in although he was 24 years old. After 2 months of oral

testosterone therapy the patient lost 9 5 lb without dieting and grew 2 in in height (fig 1, B). The pubic hair increased markedly and axillary hair appeared. The penis increased 3 cm in length and 3 cm in circumference (fig 1, D). Although no change in subjective sensations occurred, the IQ increased from 90 to 116.

This patient had received no treatment whatsoever besides sublingual testosterone. The striking improvement in growth, the loss of weight, the change of figure, the increase in size of genitalia and the augmentation of the secondary sex characteristics may be attributed to the male hormone therapy. Although the patient probably would have matured eventually without treatment, his development would have been delayed for a year or two, if not longer. Provoking and hastening the maturity has done no harm and has spared the patient much anguish and embarrassment.

**Case 7, L A, (U 78157)** The patient was first seen on Nov 6, 1941, at which time he was 21 years, 4 months old. He complained of bilateral cryptorchidism, lack of sexual development, anosmia since birth and a speech defect. He had developed slowly, had not been able to walk until the age of 3 years and had begun to talk soon thereafter. When he was 1 year old he had had an infection accompanied by convulsions. He had not attended school before he was 8 years of age and at 13 years he had reached only the third grade. Therefore he had been sent to a corrective school from which he had derived little benefit. With considerable prodding he finally had finished high school at the age of 20 years. When he was 11 years old he had been operated upon for cryptorchidism without success. At the age of 17 years he had received a series of injections once or twice a week for 1 year, the only result had been slight growth of pubic hair. He had never shaved and had never had erections or ejaculations.

The patient had narrow shoulders and disproportionately long arms and legs. His abdomen was protuberant and he had marked genu valgus. The height was 66 75 in and the weight 144 5 lb unclothed. His span was 70 in and the lower measurement, from pubis to soles, 36 75 in. He had sparse pubic and axillary hair and no beard. The penis measured 3 5 cm in length and 4 5 cm in circumference. The right testicle was pea sized and situated at the external inguinal ring. The left testicle was not felt (fig 2, C). The IQ was 75. The BMR was -10 per cent. By x ray study the bone age was estimated at 15 to 16 years, a retardation of 5 to 6 years. The sella turcica was normal.

Sublingual administration of free testosterone in propylene glycol in doses of 20 mg daily was begun on Nov 13, 1941. After 3 5 months the right testis had increased slightly in size and the left had become definitely palpable in the inguinal canal. The patient was experiencing almost constant priapism. He had not masturbated nor had he had ejaculations. The penis had increased 2 cm in length and 1 cm in circumference (fig 2, D). Since the IQ had remained approximately the same, namely 76, it was considered prudent to discontinue treatment rather than to risk producing a behavior problem in a mentally deficient individual.

This eunuchoid of 21 years of age received only free

testosterone sublingually. Both subjective and objective improvement were manifest. In view of previous experience with similar degrees of gonadal deficiency, it seems to us doubtful that 20 mg of methyl testosterone daily administered orally (that is, swallowed) would have produced as much advance in sexual maturity. Probably at least double this dose would have been required to achieve the same result.

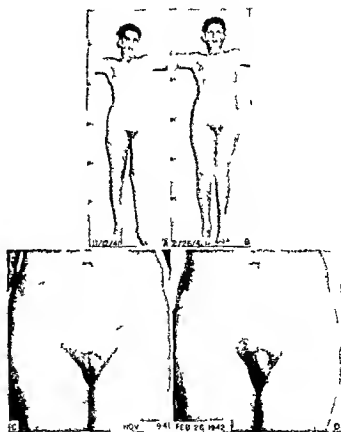


FIG 2 Case 7 L P A (78157) age 21 yr, pre adolescent eunuchoidism with cryptorchidism, treatment with testosterone sublingually. In the course of 3 months of treatment there was a growth of 1 3/4 in in height and a gain of 7 lb in weight. Note growth of penis and scrotum and increased amount of pubic hair.

**Case 8, S S, (U 72982)** The patient was first seen on June 9, 1941, at the age of 29 5 years. He complained of lack of sexual development. The penis had always been small. He had experienced erections occasionally and had attempted masturbation but had never had an ejaculation.

The patient was short (height, 62 5 in) and looked like an elderly boy. He weighed 130 lb and was plump about the waist (fig 3, A). He had no beard. The pubic escutcheon was relatively spatate and of feminine type, and the axillary hair was scant. The genitalia were infantile, the scrotum was empty, the prostate was not palpable. The penis measured 2 5 cm in length and 4 5 cm in circumference (fig 3, D).

Sublingual administration of testosterone propionate in propylene glycol in doses of 12 5 mg daily was begun on June 19, 1941. During the subsequent 3 months the patient noticed occasional twinges of pain in the right inguinal region, which may have been caused by beginning descent of the testes. In addition he had daily erections and by the third month, occasional emissions. After 7 months of treatment, Jan 8, 1942, the penis measured 3 5 cm in

<sup>2</sup> This patient was observed by Dr Evelyn Anderson who has kindly permitted us to include this case in our series.

length and 6.5 cm. in circumference (fig. 3, E). He still had daily erections and occasional ejaculations. At this time medication was changed to free testosterone in propylene glycol given sublingually in doses of 12.5 mg. daily. When the patient was seen on March 2, 1942, he had had no medication for 2 weeks. He thought the penis had regressed; however, measurements were the same as on January 8. He was last seen on April 9, 1942. At that time the penis measured 5.5 cm. in length and 7 cm. in circumference, which represents a growth of 3 cm. in length in 9.5 months of sublingual therapy. Of equal importance was the descent of the left testis into the scrotum and of the right testis to the external inguinal ring. Each testis

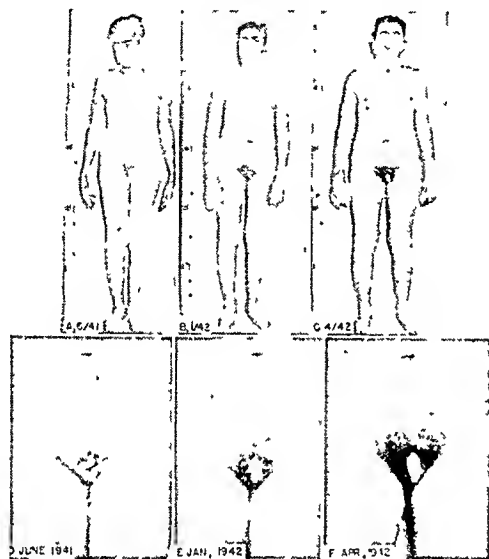


FIG. 3. Case 8. S. S. (U 72982): age 29.5 yr. Severe sexual retardation with cryptorchidism; treatment with testosterone administered sublingually, 12.5 mg., daily. Note gain of 15 lb. in weight, growth of penis and increased amount of pubic hair. Left testis descended into scrotum, right testis to external ring.

was about the size of a peanut. The pitch of the patient's voice had deepened markedly.

This patient, who was almost 30 years old when treatment was begun, was severely retarded in both primary and secondary sex characteristics and had bilateral cryptorchidism. Sublingual administration of testosterone in doses of only 12.5 mg. daily was remarkably effective both subjectively and objectively (the latter is evident in the photographs). Previous experience in comparable cases convinces us that at least 4 times this amount daily would have been required to achieve equivalent improvement if the treatment had consisted of oral ingestion of methyl testosterone.

**Case 9; C.R., (U 38241).** The patient, a 49-year-old man, was first seen on March 29, 1941. His chief complaint was diminished sexual development. In 1938 he had suffered from alcoholic polyneuritis which was severe enough to cause foot drop and slight optic atrophy. There was some residual loss of vision but the other functions were fully recovered. At about the age of 17 years, a small

amount of pubic hair as well as 20 to 30 hairs in each axilla had appeared. All the axillary hair and most of the pubic hair had fallen out a few years before we saw the patient. When he was about 30 years old, the 'peach fuzz' which had been on his forearms disappeared. At about the same time he had received some type of 'gland injections' over a 1-year period which had produced no change in his condition. Since he had never been strong enough to do heavy manual labor, he had worked as a cook or as a galley man on boats. In his association with seamen he had often followed the crowd ashore and had visited prostitutes. Although he had been able to force erections he had never had an ejaculation.

The patient was a relatively short man (height 65 in.) without beard and with marked wrinkling of the skin of his face (fig. 4, A). The outer ends of the eyebrows were very thin. Axillary hair was absent and there were only a few pubic hairs. The voice was not high-pitched. He weighed 153.25 lb. unclothed. He had a somewhat obese trunk and fairly marked gynecomastia. The penis measured 5.5 cm. in length and 6 cm. in circumference. The scrotum was small and retracted and contained 2 testes about the size of small olive pits (fig. 4, C and E). The B.M.R. was -7 per cent. Plasma cholesterol was 165 mg. per cent. The glucose tolerance curve was normal.

On April 10, 1941, testosterone propionate dissolved in propylene glycol (25 mg. per cc.) to be taken sublingually in doses of 0.1 cc. (2.5 mg.) 4 times daily, was prescribed. However, the patient took it only 3 times daily. On May 24, 1941, the error was discovered and the dose was increased to a total of 10 mg. daily. During this period no objective change occurred but the patient had 2 to 3 erections each night. By Sept. 18, 1941, the pubic hair had definitely increased (fig. 4, F). Nevertheless, the dose seemed inadequate and was increased to 25 mg. daily. On Oct. 10, 1941, 1 month later, the patient had had 2 nocturnal emissions; the penis measured 6 cm. in length and 8 cm. in circumference (fig. 4, G). Medication was changed to free testosterone in propylene glycol administered in doses of 25 mg. daily by the sublingual route. Almost immediately the patient complained of extreme restlessness and insomnia. Erections increased to 3 to 4 daily and 2 further emissions occurred in the following month. On Nov. 27, the penis measured 6 cm. in length and 8.5 cm. in circumference.

During 6.5 months of sublingual therapy with testosterone propionate, slow regrowth of pubic hair occurred and for the first time in his life the patient became conscious of libido. The penis increased 2 cm. in circumference. The tardy progress probably can be attributed to inadequate dosage. After about 5 months of treatment the patient's strength increased to such an extent that he was able to work as a stevedore. During 1 month of sublingual therapy with free testosterone there was more striking increase in pubic hair and libido. The penis increased 0.5 cm. in length and circumference.

Several circumstances interfered with this patient's therapy, so that he had no testosterone at all during January, February and March, 1942. Erections diminished in frequency but he continued to feel well. On Mar. 26, 1942, the length of the penis was 5 cm. and its circumference 8.5 cm. On this date sublingual free testosterone

therapy was resumed in doses of 25 mg daily. Two weeks later, Apr 19, the length of the penis had increased 1.5 cm and the circumference 1 cm (fig 4, H). The patient was having 3 to 4 erections daily and felt generally stronger and more vigorous.

This patient is an example of idiopathic late adult hypogonadism. Both subjective and objective improvement was obtained from sublingual testosterone therapy. For several months, while the patient was in Alaska, he could not be

previously produced and maintained in cases of severe eunuchoidism by other modes of testosterone therapy, namely by administration of testosterone propionate parenterally, by implantation of methyl testosterone pellets subcutaneously and/or by administration of methyl testosterone tablets perorally, b), initiate an improved sexual status subjectively and objectively in hypogonad individuals who had

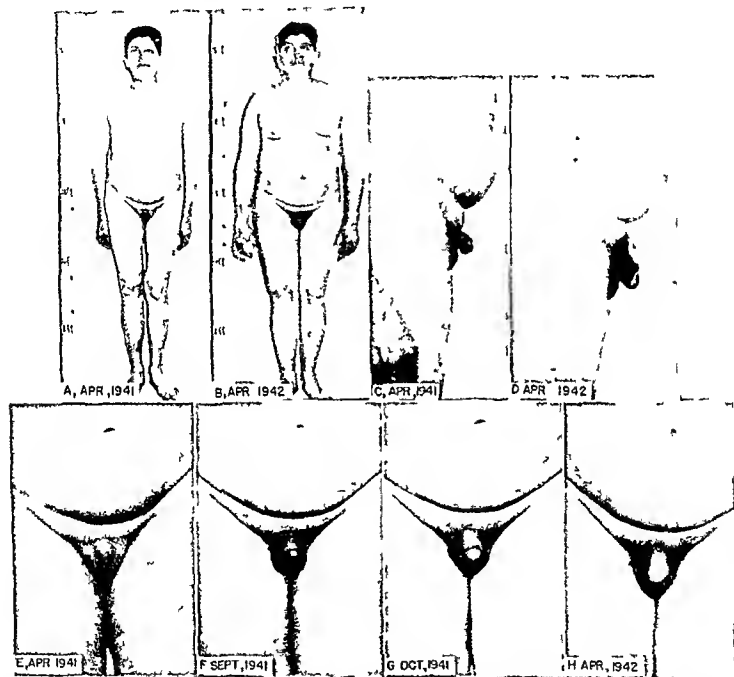


Fig 4 Case 9. C R (U 38241) age 49 yr. Idiopathic, late adult hypogonadism. Treatment with testosterone except for Jan., Feb., and most years of age), increase in size of

kept under observation and the dosage was insufficient. From previous experience we are inclined to believe that 25 mg of testosterone propionate administered parenterally three times a week would have been considerably more effective than the sublingual dose. Nevertheless, this clinical experiment with sublingual therapy produced photographically demonstrable improvement.

#### SUMMARY AND DISCUSSION

The purpose of this investigation was to determine whether various testosterone compounds administered under the tongue (sublingually) would achieve the following results: a), maintain the improvement

not previously received any form of testosterone therapy, c), reveal the advantages or disadvantages economically and otherwise of such sublingual administration as compared to parenteral, implantation or oral administration, and d), ascertain whether the methyl ester, the propionate or free testosterone (each dissolved in propylene glycol so that 0.2 cc contains 5 mg) is the most efficient. We believe that our experience in the 9 cases reported provides an adequate answer to these four considerations.

The effectiveness of testosterone compounds administered sublingually as a maintenance regime was

tested in 5 patients all of whom had been typical examples of severe preadolescent eunuchoidism and who had been exceedingly immature at the ages of 24, 24, 21, 31 and 24 years, respectively. At the time sublingual therapy was initiated they had been vastly improved by other forms of testosterone therapy. They had reached the ages of 25, 28, 26, 34, and 25 years, respectively.

A comparison of the results of sublingual and peroral therapy was made because peroral therapy had been found the simplest and most convenient means of maintaining an improved status in eunuchoids. In *case 3*, the patient's status remained the same on a sublingual dose of 10 mg. daily as it had been on a similar oral dose. In *case 1*, 20 mg. daily given sublingually were not as effective as 30 mg. given orally had been. In *case 4*, 15 mg. daily given sublingually were far less effective than 30 mg. given orally had been. In *case 5*, 15 mg. daily given sublingually proved satisfactory although it was not as stimulating as 30 mg. given orally had been. In *case 2*, 15 mg. daily given sublingually accomplished the same results as the oral dose of 30 mg. had done. For the patient in *case 2* therapy by the sublingual route was the more economical since one-half the amount of testosterone required for the oral route produced the desired effect. With this exception sublingual therapy offered no significant advantage over peroral therapy. Furthermore, these 5 patients who had had experience with other forms of testosterone therapy disliked the sublingual method because it was unpleasant and inconvenient.

The protocols and photographs of the patients in *cases 6, 7, 8 and 9*, none of whom had been treated previously with testosterone, clearly demonstrate that sublingual administration of testosterone compounds produces striking improvement with decidedly smaller dosage than would be required to accomplish equivalent results by swallowing tablets. Roughly, one-third the amount used orally will suffice by the sublingual route. This factor may be important from the economic standpoint. However, we desire to point out that 25 mg. of testosterone propionate injected intramuscularly three times a week would accomplish similar improvement more rapidly than 20 to 25 mg. daily given sublingually. Furthermore, a previous report (1) indicated that by the subcutaneous implantation of testosterone pellets only one-fifth the amount used parenterally is required.

Sublingual therapy seems to us to possess only one advantage which does not, however, apply uniformly: namely, a smaller dose is effective than by peroral therapy. Objections to the sublingual method, at least when testosterone compounds are dissolved in propylene glycol, are the unpleasant taste, the tendency

to salivation and the manifest inconvenience of holding the mouth open and the head back for several minutes without swallowing the solution. A patient could hardly be expected to submit to this procedure oftener than 5 times a day. Since the maximum dose of hormone in concentrations now available, which is at all practicable, is 0.2 cc., or 5 mg., the largest amount of hormone that can be administered sublingually in 24 hours is 25 mg.

No appreciable difference was evident between methyl testosterone and testosterone propionate when they were administered sublingually, but free testosterone in equal weights was definitely more effective than either the methyl or the propionate. All 9 patients included in this series volunteered this observation. The obvious explanation is that more androgenic substance exists in free testosterone than in an equal weight of the esters in which part of such weight is taken up by the methyl or propionic acid radicle.

#### CONCLUSIONS

1. Testosterone propionate, methyl testosterone and free testosterone, each dissolved in propylene glycol so that 0.2 cc. contained 5 mg., were administered sublingually in daily doses ranging from 10 to 25 mg.

2. Five typical eunuchoids whose condition previously had been improved and who had been successfully maintained by parenteral, implantation and/or oral administration of testosterone compounds, continued their improved states on sublingual testosterone. In only 1 of the 5 cases was the sublingual mode of therapy more economical in milligrams required than the peroral route. All the patients preferred swallowing tablets to dropping a solution under the tongue.

3. Four hypogonadal patients who had not previously received any testosterone therapy derived striking benefits subjectively and objectively from the sublingual administration of testosterone compounds. Larger oral doses of methyl testosterone would have been required to accomplish equivalent results.

4. Sublingually, free testosterone was more effective than either methyl testosterone or testosterone propionate.

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# Appraisal of Estrogenic Activity by the Vaginal Glycogen Index:

## A Comparison of Oral and Parenteral Estrone

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## [Vaginal Glycogen Index]

IN A RECENT publication (1) describing the iodine vapor method of demonstrating glycogen in human vaginal smears, this procedure<sup>1</sup> was proposed as a simple and rapid means of indicating human estrogenic response, either physiological or artificially induced. The rapidity with which a glycogen increase could be demonstrated in cases of advanced menopausal atrophy after estrone was administered parenterally and vaginally, prompted use of the test for appraising the activity of estrone by the oral route. The need for objective evidence in the human female of the comparative potency of orally and parenterally administered estrone is evident from the widely divergent data obtained from animal experiments which show "once more the difficulty of interpreting the therapeutic effectiveness of estrogens on the basis of laboratory data" (2).

Although glycogen is not always totally absent from the vaginal mucosa, even in advanced senility (3), its relative deficiency in the menopausal state as compared to the reproductive period is usually quite evident. Varying degrees of residual ovarian activity, estrogen elaboration by other endocrine organs (adrenal), or access of estrus inducing substances from ex-

trinsic sources, may account for differences observed in the menopausal mucosa. The factors which may govern the highly variable degree of vaginal involution during senility are important considerations of the menopause in general, and of atrophic vaginitis in particular.

### MATERIAL AND METHODS

In selecting the ten subjects of this study, a large group of menopausal women was investigated. The subjects were selected on the basis of vaginal atrophy characterized by advanced degrees of glycopoenia, since more glycogen indicates that some degree of estrogenic activity might still be present. Preparations for determining the glycogen index were graded as follows:

**Grade 1** Complete glycopoenia. In extreme degrees, this grade is also distinguished by marked cytopenia. The smear shows only small yellow cells of varying sizes and shapes and large amounts of amorphous cellular debris (fig. 1).

**Grade 2** Smears of this grade show a greater abundance of cells than those of grade 1. Iodine vapor staining depicts glycogen in irregular brown deposits at the cell margins or scattered irregularly throughout the cytoplasm, 'mottled cells'. Diffusely stained brown cells, usually of the small round variety, 'deep cells', may also be present in small numbers. A large number of glycopenic yellow cells is also present (fig. 2).

**Grade 3** A further increase in cell numbers is noted in this grade. The cells are larger and more regular in outline. The majority are stained diffusely throughout the cytoplasm. They have a light brown color. Non-iodophilic yellow cells are also present in abundance (fig. 3).

**Grade 4** This grade is easily recognized by the presence, almost exclusively, of large, flat, deeply stained, brown iodophilic cells present singly or in clumps. This grade represents maximal estrogenic effect and corresponds to the smear of the normal proliferative phase (fig. 4).

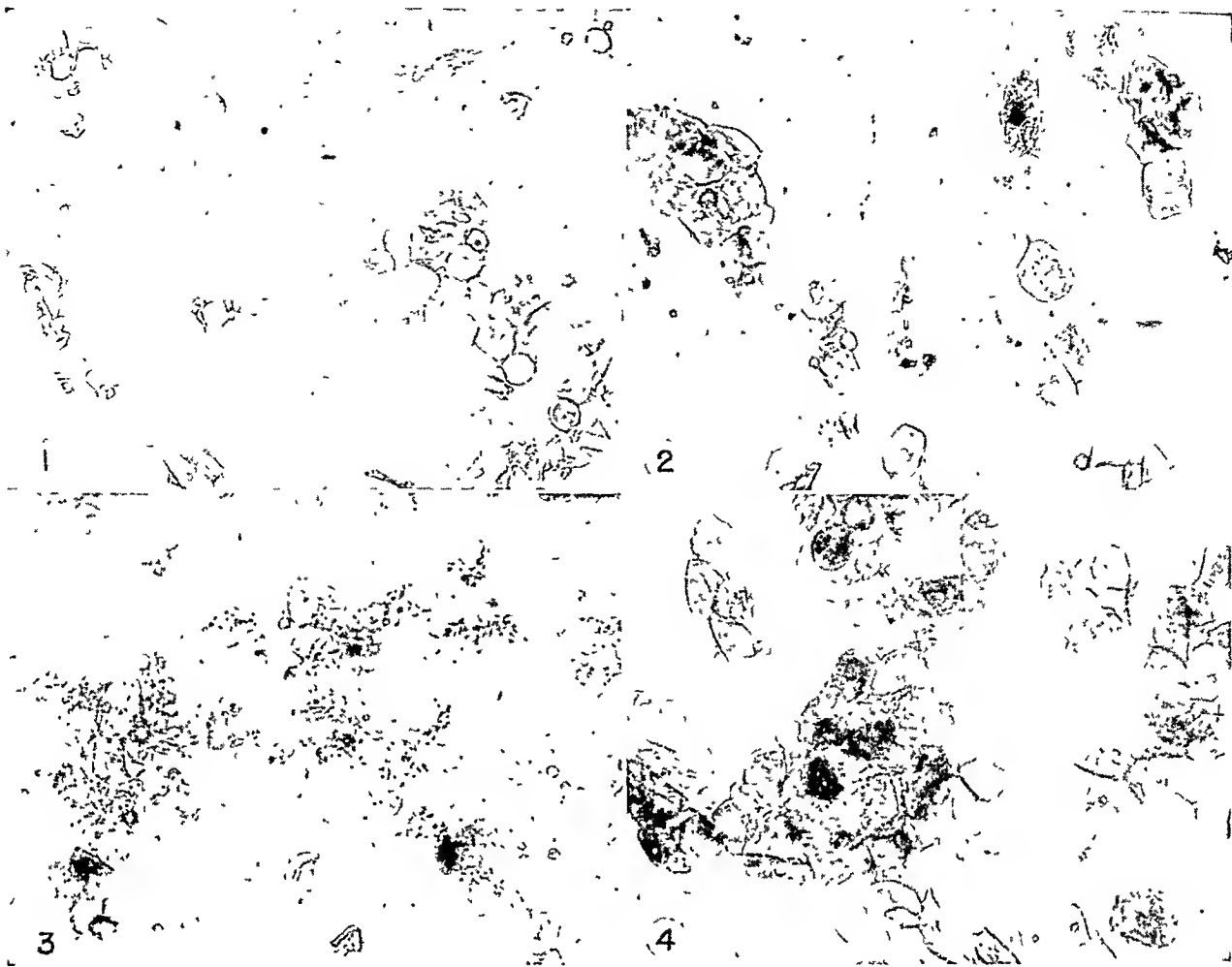
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<sup>1</sup> Iodine vapor method. a) Preparation of smears. A moistened cotton applicator is inserted into the vagina and twisted lightly  
n end  
of a  
thin

sum of cells with minimal clumping and cell distortion results. The film dries almost immediately and may be stained at once.

b) Staining of smears. Staining is accomplished simply by laying the slide, face down, over a shallow dish containing a small amount of Lugol's solution. Iodine vapors which arise insensibly from the solution suffice to stain the glycogen-containing cells in 2 or 3 minutes. Microscopic examination may be carried out immediately. Although such stains fade in 24 to 48 hours, re-staining (by the same method) may be carried out repeatedly if later examinations are desired.





VAGINAL SMEARS STAINED FOR GLYCOGEN. Fig. 1, Grade 1. Fig. 2, Grade 2. Fig. 3, Grade 3. Fig. 4, Grade 4.

**Subjects.** Ten menopausal women ranging in age from 44 to 66 years, were selected from the wards of the Tuberculosis Division of Herman Kiefer Hospital, on the basis of advanced glycopenia (grades 1 and 2).

| Patient  | Age | Menopause                   | Vaginal Smear, Glycogen Index |
|----------|-----|-----------------------------|-------------------------------|
| 1, M.N.  | 55  | Irradiation menopause, 1929 | Grade 2                       |
| 2, M.S.  | 58  | Natural menopause, 1933     | Grade 1                       |
| 3, M.R.  | 44  | Natural menopause, 1940     | Grade 2                       |
| 4, R.S.  | 59  | Natural menopause, 1930     | Grade 2                       |
| 5, M.T.  | 66  | Natural menopause, 1923     | Grade 1                       |
| 6, V.A.  | 64  | Natural menopause, 1926 (?) | Grade 2                       |
| 7, G.H.  | 48  | Natural menopause, 1939     | Grade 2                       |
| 8, D.G.  | 56  | Natural menopause, (?) yr.  | Grade 1                       |
| 9, J.G.  | 66  | Natural menopause, 1926     | Grade 1                       |
| 10, P.L. | 59  | Natural menopause, 1936     | Grade 1                       |

All were patients with various stages of advanced tuberculosis.

**Materials.** The estrone preparation used for oral administration consisted of gelatin capsules contain-

ing 0.5 mg. of crystalline estrone<sup>2</sup> dissolved in corn oil. Each capsule represented an estrogenic potency of 5000 international units.

The estrone used for parenteral administration consisted of 5.0 mg. ampules of crystalline estrone in aqueous suspension. Each ampule represented an estrogenic potency of 50,000 I.U.

**Dosages.** To compare the rapidity and the duration of effectiveness of the oral and parenteral estrone preparations prescribed, identical weighed amounts were given at different times (in six instances to the same patient) by both routes of administration. The amounts ranged from 5.0 to 15.0 mg., given in divided doses, over a five-day period, as well as in single doses, according to the following plan.

**Method.** Daily vaginal smears were made during each of the twenty observation periods, from the time of treatment until the vaginal effect had subsided, as indicated by regression of the smear to the

<sup>2</sup> The estrone preparations employed in this study were supplied through the courtesy of Parke, Davis and Company, Detroit, Mich.

| Estrone Orally                    | Estrone, Parenterally                  |
|-----------------------------------|--|
| Total amount given in single dose | Total amount given in single injection |
| 5 0 mg                            | 5 0 mg                                 |
| 7 5 mg                            | 7 5 mg                                 |
| 10 0 mg                           | 10 0 mg                                |
| 12 5 mg                           | 12 5 mg                                |
| 15 0 mg                           | 15 0 mg                                |
| In 5 equal daily doses            | In 5 equal daily injections            |
| 5 0 mg                            | 5 0 mg                                 |
| 7 5 mg                            | 7 5 mg                                 |
| 10 0 mg                           | 10 0 mg                                |
| 12 5 mg                           | 12 5 mg                                |
| 15 0 mg                           | 15 0 mg                                |

pre treatment grade Smears were stained by the 10 dme vapor technique and graded according to the system described above

To permit comparison of the oral and parenteral effects of equal dosage in the same subjects, patients 1 to 5 were given equal amounts (at different times) by both routes as single doses Patient 6 received identical amounts by both routes, in divided doses Equal amounts by both routes, in divided dosage, were given to patients 7 and 1, 8 and 3, 9 and 10, and 10 and 12 This plan was followed in order to determine the effects of individual susceptibility, 'estrogen sensitivity and estrogen resistance' (5), and the clinical status upon the resulting curves It is to be noted that while all of the patients of this series had advanced tuberculosis, only patients 2 and 5 were in critical condition

### RESULTS

The results of this study are shown in tables 1 and 2, which permit comparison of the vaginal responses to oral and parenteral estrone administrations in graduated amounts as a), single doses, and b), divided doses over a 5 day period

a) Single doses (table 1) Increases in vaginal glycogen were obtained in all instances after oral as well as after parenteral estrone administration Maximal responses (grade 4) were attained more rapidly after oral administration (average 5 4 days) than after parenteral injection (average 8 6 days) Maximal reaction after oral administration was never sustained longer than for 2 days, whereas comparable amounts injected maintained this effect for as long as 14 days The failure of large oral doses to provoke prolonged reactions is undoubtedly due to lack of assimilation or through excretory loss from the gastrointestinal tract Excretion studies (urine and feces) to determine the proportion of ingested estrone lost in this manner were not made

The effects of individual susceptibility and concomitant disease are shown in patients 2 and 5 Patient 2 had reached the terminal stages of general sized tuberculosis Studies with single oral and parenteral administrations (7 5 mg each) and, finally, 150 mg in five injections (table 2) showed progressively less response with approaching exitus It is to be noted, however, that the curves obtained for identical amounts by the two routes are strikingly similar Patient 5, who had repeatedly shown prolonged maximal responses to estrone by both routes, showed a less sustained response after 15 mg (single dose) given parenterally than did others with smaller amounts Her death at the conclusion of this trial was preceded by withdrawal bleeding

b) Divided doses, (table 2) Increases in vaginal glycogen were obtained in all instances and by both routes Oral administration of estrone in divided doses produced maximal reaction as rapidly (average 6 2 days) as did the parenteral method (average 7 days) Sustained maximal effects with divided

TABLE 1 GRADED RESPONSES IN VAGINAL GLYCOGEN INDEX TO ESTRONE GIVEN IN SINGLE DOSES

| Route of Administration | Patient Number | Estrone mg | Grade of Vaginal Glycogen Index on Days |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |          |    |    |    |    |    |    |    |    |   |
|-------------------------|----------------|------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----------|----|----|----|----|----|----|----|----|---|
|                         |                |            | 1                                       | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19       | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |   |
| Oral                    | 1              | 5 0        | 2                                       | 2 |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |          |    |    |    |    |    |    |    |    |   |
| Parenteral              | 1              | 5 0        | 2                                       | 2 | 2 | 2 | 2 | 3 | 3 | 4 | 4 | 4  | 3  | 3  | 3  | 2  | 3  | 2  | 2  | 2  | 2        | 2  |    |    |    |    |    |    |    |   |
| Oral                    | 2              | 7 5        | 1                                       | 1 | 1 | 3 | 2 | 3 | 3 | 4 | 4 | 3  | 2  | 3  | 3  | 2  | 2  | 1  | 1  | 1  | 1        |    |    |    |    |    |    |    |    |   |
| Parenteral              | 2              | 7 5        | 1                                       | 1 | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 3  | 3  | 2  | 3  | 3  | 4  | 3  | 2  | 3  | 2        | 1  | 1  | 1  | 1  | 1  | 1  | 1  |    |   |
| Oral                    | 3              | 10 0       | 2                                       | 2 | 2 | 3 | 4 | 3 | 3 | 2 | 2 | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2        |    |    |    |    |    |    |    |    |   |
| Parenteral              | 3              | 10 0       | 2                                       | 2 | 2 | 2 | 3 | 4 | 4 | 4 | 4 | 4  | 4  | 4  | 4  | 4  | 3  | 3  | 1  | 1  | 1        | 1  |    |    |    |    |    |    |    |   |
| Oral                    | 4              | 12 5       | 2                                       | 2 | 2 | 2 | 2 | 3 | 4 | 4 | 3 | 3  | 3  | 3  | 2  | 1  | 2  | 2  | 2  | 2  | 2        |    |    |    |    |    |    |    |    |   |
| Parenteral              | 4              | 12 5       | 2                                       | 2 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 4  | 4  | 4  | 4  | 4  | 4  | 4  | 4  | 4  | 4        | 4  | 4  | 4  | 4  | 4  | 3  | 2  | 3  | 2 |
| Oral                    | 5              | 15 0       | 2                                       | 2 | 3 | 2 | 4 | 4 | 3 | 3 | 2 | 2  | 2  | 1  | 1  | 1  | 1  |    |    |    |          |    |    |    |    |    |    |    |    |   |
| Parenteral              | 5              | 15 0       | 1                                       | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 4 | 4  | 4  | 4  | 4  | 3  | 3  | 2  | 2  | 3  | (Exitus) |    |    |    |    |    |    |    |    |   |

Figures in boldface represent grade of glycogen index on day of treatment

TABLE 2. GRADED RESPONSES IN VAGINAL GLYCOGEN INDEX TO GRADUATED AMOUNTS OF ESTRONE GIVEN IN DIVIDED DOSES

| Route of Administration | Patient Number | Estrone, mg. | Grade of Vaginal Glycogen Index on Days |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |  |
|-------------------------|----------------|--------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|----------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--|--|
|                         |                |              | 1                                       | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |   |   |   |          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |  |
| Oral<br>Parenteral      | 6<br>6         | 5.0          | 2                                       | 2 | 3 | 4 | 4 | 4 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 4  | 4  | 4  | 4 | 4 | 3 | 3        | 4 | 3 | 3 | 3 | 3 | 2 | 2 |   |   |   |   |   |   |   |   |  |  |
|                         |                | 5.0          | 2                                       | 2 | 2 | 3 | 3 | 3 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 3  | 3  | 4  | 4 | 4 | 4 | 4        | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 2 | 3 | 3 | 3 | 2 | 2 |  |  |
| Oral<br>Parenteral      | 7<br>1         | 7.5          | 2                                       | 1 | 2 | 2 | 2 | 3 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 3  | 4  | 4  | 4 | 3 | 3 | 2        | 3 | 2 | 2 | 2 | 2 | 2 | 2 |   |   |   |   |   |   |   |   |  |  |
|                         |                | 7.5          | 3                                       | 3 | 2 | 1 | 3 | 4 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 4  | 4  | 4  | 4 | 4 | 4 | 4        | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 3 | 2 | 2 | 2 | 2 |   |  |  |
| Oral<br>Parenteral      | 8<br>3         | 10.0         | 1                                       | 1 | 1 | 1 | 1 | 2 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 3  | 4  | 4  | 3 | 1 | 1 | 1        | 2 | 1 | 1 | 1 | 1 | 1 | 1 |   |   |   |   |   |   |   |   |  |  |
|                         |                | 10.0         | 1                                       | 1 | 2 | 2 | 2 | 3 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 3  | 4  | 4  | 4 | 4 | 3 | 3        | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |   |  |  |
| Oral<br>Parenteral      | 9<br>10        | 12.5         | 1                                       | 2 | 2 | 2 | 3 | 3 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 4  | 4  | 4  | 4 | 3 | 3 | 3        | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 |   |   |   |   |  |  |
|                         |                | 12.5         | 2                                       | 1 | 1 | 2 | 1 | 3 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 3  | 4  | 4  | 4 | 4 | 3 | 1        | 3 | 3 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 1 |   |  |  |
| Oral<br>Parenteral      | 10<br>2        | 15.0         | 1                                       | 1 | 2 | 2 | 2 | 2 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 2  | 3  | 3  | 4 | 4 | 4 | 4        | 4 | 3 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 |   |   |   |   |   |  |  |
|                         |                | 15.0         | 1                                       | 1 | 1 | 1 | 2 | 2 |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 3  | 2  | 2  | 2 | 2 | 1 | (Exitus) |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |  |

Figures in boldface represent grades of glycogen index on days of treatment.

dosage were more nearly equal than were those obtained from single doses. This difference is probably explained by diminished excretory loss. Patient 6, a highly estrogen sensitive subject, showed remarkably prolonged maximal reactions to both methods of administration. All subjects of this group (with the exception of patient 2) were in reasonably good condition. The corresponding curves for oral and parenteral administration are closely parallel with the one exception noted (2).

**Toxicity.** No toxic manifestations (nausea, vomiting) resulted from the oral administration of estrone, nor were any untoward effects noted upon the existing tuberculosis. No attempt was made to correlate vaginal smear changes with the effects of therapy upon menopausal symptoms.

SUMMARY

A group of 10 menopausal women with advanced vaginal atrophy, as indicated by marked glycopenia, received graduated doses of estrone by oral and parenteral administration. The effects of identical amounts, given in single or equally divided doses, were determined from daily vaginal smears stained for glycogen by the iodine vapor method. Evidence is presented which indicates that oral administration of estrone induces vaginal glycogen increases identical with those following parenteral administration of the same amounts. Maximal vaginal effects were obtained more promptly after oral than after parenteral administration. More prolonged effects were obtained with divided daily doses than from single large doses when given by mouth. Lack of assimilation through excretory loss from the gastrointestinal tract is offered as an explanation of the lack of greater effectiveness of large oral doses. Parenterally administered

estrone in single doses exerted a less prompt, though more prolonged effect; when equal amounts were given in divided doses the sustained action by both routes was more nearly equal. Variations of individual susceptibility and the influence of concomitant disease appear to influence the intensity of the vaginal glycogen response. No toxic effects (nausea, vomiting) were noted in any patient after oral administration.

CONCLUSIONS

1. Vaginal glycogen content, as demonstrated by the iodine vapor method of staining vaginal smears, is a sensitive index of estrogenic activity in the human subject.
2. Estrone when given orally is highly effective in augmenting the glycogen content of the vaginal mucosa.
3. Estrone is neither destroyed in the gastrointestinal tract nor sufficiently altered in its metabolism to interfere with its estrogenic effect upon the vaginal epithelium.
4. The promptness with which estrogenic effect follows the administration of estrone by mouth, and the ability of the oral route to sustain maximal effects by daily doses, suggest that this method can supplant parenteral injections in estrogen therapy.
5. Lack of toxic reactions in this series suggests the use of oral estrone, especially when synthetic products are not tolerated.

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# Glycogen Studies on Human Endometrium:

Correlation of Quantitative Chemical Estimation and the Qualitative Demonstration by Histological Methods

## [Endometrial Glycogen]

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THE QUANTITATIVE estimation of glycogen in the endometrium was first made by Van Slyke and Chen (1) in 1936, using the female micrque. They stated that there was an increase in glycogen in the differentiative stage over that of the proliferative stage, noting that in the proliferative stage the endometrium contained 0.3 gm per cent, the differentiative phase 0.53 gm per cent of glycogen and that on the first day of ovulatory menstruation there was an even slightly higher increment.

Zondek, in 1940 (2, 3) noted the same relationship in human endometrium. He reported 0.38 gm per cent in the proliferative phase, 0.47 in the interval phase, and 0.427 gm per cent of glycogen in the differentiative stage.

Randall and Power, in 1942, (4) estimated the glycogen content of human endometrium taken by curettage; they noted in the late proliferative phase an average of 0.171 gm per cent, in the early differentiative phase, an average of 1.09, and in the late differentiative phase, an average of 0.71 gm per cent of glycogen.

In order to investigate further these slightly divergent results and to correlate, if possible, the amount of chemically demonstrable glycogen for a given sample of endometrium with that shown by histological methods, the following investigation was undertaken.

### METHODS

Thirty-three specimens of human endometrium were analyzed quantitatively for the glycogen content and corresponding blocks of tissue were stained for glycogen and controlled by mucin staining in

serial sections. These specimens were furnished from operative cases in which hysterectomy was done and the whole uterus was available. This afforded ample material for chemical and histochemical studies.

The uterus was obtained from surgery was immediately opened and blocks of the endometrium for the histochemical procedures fixed in absolute alcohol. The rest of the endometrium was carefully scraped from the myometrium with a dull spoon, care being used not to include any myometrial tissue. This was immediately transferred to the freezing microtome and frozen solid in a stream of carbon dioxide, chipped off into a tared watch glass and weighed. After weighing, the frozen tissue was transferred to a 50 cc Erlenmeyer pyrex flask containing 5 cc of 75 per cent potassium hydroxide, shaken well, and placed on the boiling water bath under a cold water reflux condenser for 3 hours. At the end of this time the sample was neutralized with concentrated hydrochloric acid, and 5 cc of 2.2 per cent hydrochloric acid was added. The conversion was allowed to act for 3 hours.

At the end of this time the sample was again neutralized with 0.275 per cent sodium hydroxide and the glucose determination carried out according to the technique of Miller and Van Slyke (5). Aliquots whose titration showed no glucose were tested for carbohydrate by the phenylhydrazine hydrochloride reaction and the resorcin hydrochloride test for simple sugars.

The blocks of endometrium for histochemical determinations were fixed in absolute alcohol, and successively transferred to 80 per cent alcohol, acetone and paraffin. Serial sections were mounted, one series being stained with Delafield's hematoxylin and Best's carmalum for glycogen, and the other with Delafield's hematoxylin and Mayer's mucicarmine for mucin.

The phases of endometrial development in the various specimens were dated from the first day of menstrual flow in conformity with the terminology used by Zondek and Stein (2), and by Randall and Power (4). The stage of active regeneration following the menstrual flow was designated as proliferative. The stage immediately following this, in which there appears histologic evidence of glycogen formation, has been designated as the interval stage; this pattern is

cleus toward the central position of the cell. Such glycogen was designated as basal. Increasing accumulations of glycogen were found to extend toward the distal or luminal end of the cell, occupying a position lateral to the nucleus, and were designated as being in the transitional position. Later this glycogen accumulated at the luminal or distal portion of the epithelial cell and the nucleus again assumed a basal position. Small amounts of the luminal glycogen were

TABLE 1. CHEMICAL DETERMINATION AND HISTOLOGICAL ESTIMATION OF GLYCOGEN IN HUMAN ENDOMETRIUM

| Endometrial Stage     | Chemical Determinations |                |   |   | Histological Estimations      |       |                            |       |
|-----------------------|-------------------------|----------------|---|---|-------------------------------|-------|----------------------------|-------|
|                       | Weight sample, gm.      | Glycogen mg. % | P | R | Amount of glycogen stained in |       | Amount of Mucin Stained in |       |
|                       |                         |                |   |   | Cells                         | Lumen | Cells                      | Lumen |
| Early proliferative   | 0.140                   |                | o | o | o                             | o     | o                          | 3+    |
| Early proliferative   | 0.059                   | 88             |   |   | o                             | o     | o                          | 3+    |
| Early proliferative   | 0.542                   | 240            |   |   | o                             | o     | o                          | 1+    |
| Early proliferative   | 0.408                   | 63             |   |   | o                             | o     | o                          | 1+    |
| Early proliferative   | 0.632                   | 114            |   |   | o                             | o     | o                          | 1+    |
| Early proliferative   | 0.632                   | 114            |   |   | o                             | o     | o                          | 1+    |
| Early proliferative   | 0.345                   | 336            |   |   | o                             | o     | o                          | 1+    |
| Mid proliferative     | 0.307                   | 186            |   |   | 1+, basal                     | o     | o                          | 3+    |
| Mid proliferative     | 0.830                   |                | o | o | o                             | o     | o                          | 3+    |
| Mid proliferative     | 0.775                   |                | o | o | 1+, basal                     | o     | o                          | 4+    |
| Mid proliferative     | 0.220                   | 180            |   |   | 1+, basal                     | o     | o                          | 1+    |
| Mid proliferative     | 0.930                   | 147            |   |   | 1+, basal                     | o     | o                          | 2+    |
| Mid proliferative     | 0.378                   | 404            |   |   | 1+, basal                     | o     | o                          | 2+    |
| Mid proliferative     | 0.762                   |                | o | o | o                             | o     | o                          | 2+    |
| Mid proliferative     | 3.435                   | 47             |   |   | o                             | o     | o                          | 1+    |
| Mid proliferative     | 0.964                   | 138            |   |   | o                             | o     | o                          | o     |
| Mid proliferative     | 0.856                   | 142            |   |   | o                             | o     | o                          | 1+    |
| Mid proliferative     | 1.151                   | 123            |   |   | o                             | o     | o                          | 1+    |
| Mid proliferative     | 0.122                   | 62             |   |   | 1+, basal, distal             | o     | o                          | 2+    |
| Mid proliferative     | 0.442                   | 387            |   |   | 1+, basal                     | o     | o                          | 3+    |
| Late proliferative    | 2.664                   | 231            |   |   | 1+, basal                     | o     | o                          | 3+    |
| Late proliferative    | 2.899                   | 308            |   |   | 3+, basal, distal             | o     | o                          | 4+    |
| Early interval        | 1.390                   | 527            |   |   | 3+, basal, distal             | o     | o                          | 4+    |
| Mid interval          | 0.590                   | 236            |   |   | 2+, basal                     | o     | o                          | 3+    |
| Mid interval          | 0.354                   | 293            |   |   | 2+, basal, distal             | o     | o                          | 2+    |
| Mid interval          | 0.932                   | 66             |   |   |                               |       |                            |       |
| Mid interval          | 1.024                   | 56             |   |   | 1+, basal, distal             | o     | o                          | 4+    |
| Early differentiative | 2.490                   | 93             |   |   | 1+, distal                    | o     | o                          | 4+    |
| Early differentiative | 0.550                   | 303            |   |   |                               |       | o                          | 1+    |
| Mid differentiative   | 1.474                   | 924            |   |   | 2+, basal distal              | o     | o                          | 4+    |
| Late differentiative  | 1.550                   |                | o | o | o                             | o     | o                          | 4+    |
| Late differentiative  | 0.585                   | 239            |   |   | o                             | o     | o                          | 4+    |
| Late differentiative  | 0.200                   | 570            |   |   | 1+, basal                     | o     | o                          | 4+    |
| Late differentiative  | 1.362                   | 23             |   |   | o                             | o     | o                          | 3+    |

P, phenylhydrazine test; R, resorcin-HCl test.

identical with that of endometrial development which is sometimes designated as ovulatory. The stage of distinct post-ovulatory differentiation follows this interval stage. Further descriptive limitations may be placed on these various stages by applying the terms early, mid or late.

The position of stained glycogen in the epithelium of the endometrial gland was designated by its location relative to the nucleus of the individual epithelial cell. The first or earliest position was at the base of the cell adjacent to the basement membrane, in which position the glycogen apparently displaced the nu-

occasionally extruded as globules into the lumen of the gland.

RESULTS

In table 1 are shown the endometrial stage, the weight of the sample, the grams of glycogen per 100 gm. of tissue, the results of the phenyl-hydrazine-HCl reaction and the resorcin-HCl test, the qualitative estimate and the position of the glycogen and mucin in the stained sections.

*Proliferative and interval phases.* There were 6 specimens in the early proliferative stage which

showed a glycogen content ranging from zero to 0.336 gm per cent and averaging 0.141 gm per cent. No glycogen was demonstrated histologically in the glandular or surface epithelium by the oil immersion lens at 900 diameters. The mucin control sections had been made to determine the amount of error due to the reaction of mucin with acid stains and to see if glycogen stained as mucin or if it was possible to stain mucin as glycogen. Also it was desired to determine if glycogen and mucin occupied the same position in the cell and gland lumen. The glycogen

The progressive increase of the glycogen content is illustrated in a late proliferative specimen containing 0.2314 gm per cent of glycogen. This tissue, on section, showed a slight amount of basal glycogen and large amounts of mucin in the lumen of the gland.

A late proliferative early interval specimen contained 0.2087 gm per cent of glycogen, histologically, large amounts of glycogen appeared in the basal and distal positions of the gland cells. Very large amounts of mucin were found in the lumen of these glands.

One specimen representing the early interval phase

TABLE 2 CORRELATION OF THE DAY OF THE MENSTRUAL CYCLE WITH THE ENDOMETRIAL STAGE, AND QUANTITIES OF GLYCOGEN OBTAINED BY VARIOUS INVESTIGATORS

| Day of Menstrual | Endometrial Stage                  | Randall & Power     |                |     |         | Zondek & Stein      |                |     |         | Spyker & Fidler     |                |     |         |
|------------------|------------------------------------|---------------------|----------------|-----|---------|---------------------|----------------|-----|---------|---------------------|----------------|-----|---------|
|                  |                                    | Number of specimens | Glycogen, mg % |     |         | Number of specimens | Glycogen, mg % |     |         | Number of specimens | Glycogen, mg % |     |         |
|                  |                                    |                     | Max            | Min | Average |                     | Max            | Min | Average |                     | Max            | Min | Average |
| 9                | Early proliferative                |                     |                |     |         | 2                   | 8              | 0   | 4       | 6                   | 34             | 0   | 14      |
| 10               | Early proliferative                |                     |                |     |         | 3                   | 25             | 0   | 8       |                     |                |     |         |
| 11               | Mid proliferative                  | 1                   | 18             |     |         |                     |                |     |         | 12                  | 40             | 0   | 12      |
| 13               | Late proliferative                 |                     |                |     |         |                     |                |     |         | 1                   | 39             |     |         |
| 14               | Late proliferative                 | 2                   | 26             | 0   | 19      | 1                   | 10             |     |         | 1                   | 23             |     |         |
| 15               | Early interval                     | 1                   | 113            |     |         |                     |                |     |         | 1                   | 21             |     |         |
| 16               | Early interval                     | 1                   | 15             |     |         |                     |                |     |         | 1                   | 52             |     |         |
| 17               | Mid interval                       | 4                   | 126            | 23  | 77      | 1                   | 99             |     |         | 4                   | 29             | 6   | 16      |
| 18               | Mid interval                       |                     |                |     |         | 1                   | 21             |     |         |                     |                |     |         |
| 19               | Mid interval                       | 1                   | 44             |     |         | 7                   | 47             | 7   | 31      |                     |                |     |         |
| 20               | Late interval                      | 2                   | 65             | 36  | 51      | 1                   | 7              |     |         |                     |                |     |         |
| 21               | Late interval                      | 3                   | 69             | 38  | 51      | 2                   | 52             | 47  | 49      |                     |                |     |         |
| 22               | Early differentiative              | 3                   | 168            | 57  | 100     | 1                   | 15             |     |         | 2                   | 30             | 9   | 20      |
| 23               | Early differentiative              | 5                   | 104            | 53  | 81      | 6                   | 49             | 8   | 41      |                     |                |     |         |
| 24               | Mid differentiative                | 1                   | 51             |     |         | 3                   | 28             | 8   | 28      |                     |                |     |         |
| 25               | Mid differentiative                | 3                   | 102            | 51  | 71      | 4                   | 56             | 5   | 43      | 1                   | 92             |     |         |
| 26               | Late differentiative               | 1                   | 37             |     |         | 8                   | 43             | 16  | 37      |                     |                |     |         |
| 27               | Late differentiative               | 1                   | 88             |     |         | 4                   | 81             | 15  | 66      | 4                   | 57             | 0   | 21      |
| 28               | Late differentiative               | 2                   | 72             | 52  | 62      | 1                   | 13             |     |         |                     |                |     |         |
| 29               | Late differentiative               |                     |                |     |         | 1                   | 53             |     |         |                     |                |     |         |
| 30               | Late differentiative               |                     |                |     |         | 1                   | 31             |     |         |                     |                |     |         |
|                  | Atrophic                           | 1                   | 20             |     |         |                     |                |     |         |                     |                |     |         |
| 49               | Late differentiative 'Anovulatory' | 1                   | 85             |     |         | 6                   | 16             | 0   | 8       |                     |                |     |         |

was found entirely within the glandular epithelial cell and at its base, the mucin was found in from slight to large amounts in the lumen of the gland and in the uterine cavity.

Zondek has stated (3) that no glycogen has yet been detected in the uterine mucosa of human subjects during the phase of follicular maturation, by means of histochemical methods. In this series there were 12 specimens in the mid-proliferative stage containing glycogen, ranging from zero to 0.404 gm per cent and averaging 0.110 gm per cent. The glycogen in this stage was histologically demonstrable in small amounts, or not at all. It usually consisted of fine or coarse granules and was located immediately above or below the nucleus. None was found in the lumen of the gland. Mucin was present in the lumen of the glands.

contained 0.5274 gm per cent of glycogen and, on section, large amounts of basal and distal granules of glycogen were demonstrated. Mucin was present in very large amounts.

A decrease of the glycogen content is illustrated in 4 mid-interval specimens of endometrium which contained glycogen ranging from 0.2931 to 0.0561 gm per cent and averaging 0.1603. Slight to moderate amounts of basal and distal glycogen were demonstrated histologically with moderate to very large amounts of mucin in the lumen of the glands.

*Differentiative or secretory phases.* Two early differentiative specimens of endometrium contained glycogen ranging from 0.3039 to 0.0930 gm per cent and averaging 0.1984, which is a higher level than is found in the proliferative phase. Slight amounts of glycogen in the distal portion of the gland epithelium

were demonstrated in histologic sections and slight to very large amounts of mucin in the lumen of the glands.

Four late-differentiative samples contained glycogen ranging from zero to a maximum of 0.57 gm. per cent and averaging 0.2081, thus maintaining a higher level than was found in the proliferative phase. The sections showed none to slight amounts of stained glycogen in the glandular epithelium and a moderate amount in the epithelial cells of the surface epithelium. There were large to very large amounts of mucin in the lumen of the glands.

The chemical reactions for carbohydrate, especially glucose, with phenylhydrazine and resorcin hydrochloride, were made on all aliquot samples giving a negative quantity for glucose in the titration with ceric sulphate.

The data in table 2 represents an attempt to correlate the day of the menstrual cycle with the phase of histologic development of the endometrium, by comparing the quantitative amounts of glycogen reported by Randall and Power, by Zondek and Stein, and our data. Randall and Power found the highest percentage of glycogen on day 22, the lowest on day 14. They obtained consistently high values for specimens from the 17th to 28th days. These were, on an average, well above the estimations on specimens from days 1 to 17. Zondek and Stein obtained the highest glycogen percentage in endometrium obtained on day 17, the lowest on days 9 and 10 and in those from patients with anovulatory cycles. The specimens of endometrium in the differentiative stage contained more glycogen than those in the proliferative stage.

In the series of studies in our laboratory the highest glycogen percentage was obtained in the mid-differentiative phase of the endometrial cycle, the lowest in the early proliferative and late differentiative stages. High values for glycogen were obtained in some specimens from the proliferative, interval and differentiative phases of the menstrual cycle, although several samples from each phase showed low values. In this study there was little evidence of the association of the presence of high, medium and low quantities of glycogen in relation to the phases of the cycle as compared with the reports of other workers. The quantities of glycogen in the tissues of the differentiative phase were, on an average, higher than those of the proliferative stage.

#### COMMENTS

It is noted that graphs of the glycogen content of the endometrium do not coincide particularly with

any reported hormone levels influencing the endometrium, but instead, follow these factors by 1 to 3 days. Roughly, the highest percentage of glycogen found by Randall and Power was on day 15 and the curve remained at a higher level in the differentiative phase than in the proliferative phase. There was a second rise in this graph line on day 23 and the level following this was still higher than either of the two preceding levels. Zondek and Stein found low glycogen levels in the proliferative phase, with a peak on day 17 and a sustained level in the differentiative phase which was higher than that in the proliferative stage. Our results show low levels in the proliferative phase with a peak in the mid-proliferative phase, one in the early interval and one in the mid-differentiative phase. The level in the differentiative phase was slightly higher than that of the proliferative phase.

#### SUMMARY AND CONCLUSIONS

1. From these comparisons the conclusion can be made that proliferative endometrium contains at most only slight amounts of glycogen.
2. In the interval phase the values for glycogen content of the endometrium are increased sharply.
3. There is a postovulatory peak of glycogen content which occurs at about the 15th to 20th day of the cycle.
4. In the differentiative phase, the endometrium contains quantities of glycogen in excess of that in the proliferative stage.
5. The presence of mucin seems to be independent of the hormonal influence. It is relatively less in a stage in which the glycogen metabolism is more normal and is increased in cystic modifications of the endometrium. Mucin was never demonstrated within the cells but only in the lumen of the gland or in the uterine cavity.
6. Glycogen is found chiefly in the epithelial cells of the glands and surface, but it may appear in the gland lumen during the interval and late differentiative phases and also in the uterine cavity.
7. The presence of glycogen in the stroma was rarely evident.

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# Effects of Contraphysiologically Administered Diethylstilbestrol on the Menstrual Cycle<sup>1</sup>

## [Diethylstilbestrol and Normal Menstrual Cycle]

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NUMEROUS workers have reported that the intermenstrual administration of hormonal estrogens in relatively large doses results in an 'over-riding' of corpus luteum function. Our group, using in this fashion moderate doses of hormonal estrogens in women with normal ovarian function, observed no depressing effects upon corpus luteum function (1).

Since the non hormonal estrogen, diethylstilbestrol, is available at low cost, its clinical use has been widespread. Unfortunately many of its applications have been and continue to be uncritical. In view of these facts it seemed worth while to investigate the effects of the contra-physiologic use of moderately small doses of diethylstilbestrol in women with normal ovarian function. The present communication deals with this investigation.

### METHODS

Thirteen patients in whom episodes of bleeding occurred from a progestational endometrium were chosen for these studies. Their ages ranged from 18 to 32 years and averaged 25.5 years.

Diethylstilbestrol<sup>2</sup> was administered orally in daily amounts ranging from 1 to 6 mg. Treatment was given to 12 patients for 10 days during the first half of the menstrual cycle, from the 5th to the 14th day inclusive. In the case of one patient, who received therapy during 4 menstrual cycles, treatment was

begun on the 5th day and ended on the 24th day of each cycle.

Four patients received treatment during a single cycle, 5 patients during 2 consecutive cycles each, 2 patients during 3 consecutive cycles each and 2 patients each received treatment during 4 consecutive menstrual cycles.

The endometrium was sampled for study prior to and during treatment. Similar studies, made during menstrual cycles subsequent to therapy, permitted evaluation of persistent effects of therapy. Endometrial biopsies were obtained within the first 24 hours after the onset of episodes of bleeding. Classification of endometrial responses was made by one of us (E.C.H.).

Data upon the length of the cycle and the duration and amount of bleeding before, during and following therapy were analyzed.

Studies of the urinary excretion of sodium pregnanediol glucuronide in 6 patients were made prior to and during therapy. The method of Vinning was employed (2).

All patients had complete medical, gynecologic and endocrine surveys, including determinations of the basal metabolic rate and roentgenograms of the sella turcica.

### DATA

The immediate effects of diethylstilbestrol were studied during a total of 32 cycles, the remote effects during another 23 cycles.

**Dosage schedules** The daily dosage and the days of therapy, with relation to the menstrual cycle, were distributed as follows.

1 mg., 5th to 14th days inclusive, 10 patients, 26 cycles  
1 mg., 5th to 24th days inclusive, 1 patient, 1 cycle

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<sup>2</sup> Part of the expenses of these studies was defrayed by grants to one of us (E.C.H.) from the Research Council of Duke University and from Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.

<sup>3</sup> Estroben, supplied by Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.



2 mg., 5th to 14th days inclusive; 1 patient, 1 cycle  
2 mg., 5th to 24th days inclusive; 1 patient, 1 cycle  
3 mg., 5th to 24th days inclusive; 1 patient, 2 cycles  
6 mg., 5th to 14th days inclusive; 1 patient, 1 cycle

*Effect upon endometrium.* The endometrial responses were studied in 15 of the 32 cycles during which therapy was given to 9 of the 13 patients under treatment. In all but one instance, these studies were

TABLE 1. SUMMARY OF SERIES OF CONSECUTIVE TREATMENT CYCLES AND OF THE ENDOMETRIAL RESPONSES IN 15 CYCLES SAMPLED

| Pa-<br>tient | Series | Consecutive Cycles of Therapy      |                       |                       |                       |
|--------------|--------|------------------------------------|-----------------------|-----------------------|-----------------------|
|              |        | 1                                  | 2                     | 3                     | 4                     |
| 1            | 1      | Persistent estrogenic              |                       |                       |                       |
| 2            | 1      | Persistent estrogenic              |                       |                       |                       |
| 3            | 1      | Marked progestational              | None                  |                       |                       |
| 4            | 1      | Progestational                     | None                  |                       |                       |
| 5            | 1      | None                               | Persistent estrogenic |                       |                       |
| 6            | 1      | Persistent estrogenic              | None                  | Persistent estrogenic |                       |
| 7            | 1      | Persistent estrogenic              | Persistent estrogenic | Persistent estrogenic |                       |
| 8            | 1      | Progestational                     | None                  |                       |                       |
| 9            | 2      | Persistent estrogenic <sup>1</sup> |                       |                       |                       |
|              | 1      | None                               |                       |                       |                       |
|              | 2      | None                               |                       |                       |                       |
| 10           | 3      | None                               | Progestational        | Persistent estrogenic | Marked progestational |
|              | 1      | None                               |                       |                       |                       |
| 11           | 2      | None                               |                       |                       |                       |
| 12           | 1      | None                               | None                  |                       |                       |
| 13           | 1      | None                               | None                  | None                  | None                  |

<sup>1</sup> Following 2 mg. of diethylstilbestrol daily from 5th to 14th days inclusive.

made after therapy which consisted of 1 mg. of diethylstilbestrol daily from the 5th to the 14th days of the cycle. Two-thirds of the specimens of endometrium were estrogenic in type, while one-third were progestational (table 1).

Endometrial studies were made on 3 patients during a total of 13 cycles subsequent to the cessation of therapy. Twenty per cent of the specimens were estrogenic in character, while 80 per cent were progestational in type (table 2). These follow-up studies were made on patients who had been previously treated during 2 to 4 consecutive cycles.

*Effects upon length of the cycle.* There was consistent shortening of the cycles in 5 patients, the average length being reduced from 29.6 days prior to therapy, to 20.3 days during treatment. The cycles of 2 pa-

tients were consistently lengthened during therapy, the average being increased from 25.4 days prior to therapy to 38.2 days during treatment. Alterations in the length of the cycles of 5 patients were not constant in any one direction. The average length of the cycle of these patients prior to therapy was 28 days and during treatment was 27.6 days. There was no significant change in the length of the cycles of one patient during therapy.

Subsequent to the cessation of diethylstilbestrol therapy 3 patients, who had had consistently shortened cycles during therapy, were investigated for 13 cycles. The average length of these was 29.1 days. The average length before and during treatment had been 26.8 and 21.2 days, respectively. Nine cycles of 4 patients, who had had varying alterations in the length of cycles during therapy, averaged 25.6 days in length following cessation of treatment. Prior to and during treatment the average length was 27.9 and 28.7 days, respectively. Variations in the length of the cycles, as well as other pertinent data, of 2 of these patients, are given in figures 1 and 2.

Only one episode of uterine bleeding occurred concomitantly with therapy. In this instance, bleeding began on the 3rd day of treatment and terminated

TABLE 2. SUMMARY OF SERIES OF CONSECUTIVE CYCLES INVESTIGATED FOLLOWING THERAPY AND OF THE ENDOMETRIAL FINDINGS IN 11 CYCLES SAMPLED

| Pa-<br>tient | Series<br>of<br>Treat-<br>ment | Consecutive Cycles Following Therapy |                       |                |                         |
|--------------|--------------------------------|--------------------------------------|-----------------------|----------------|-------------------------|
|              |                                | 1                                    | 2                     | 3              | 4                       |
| 6            | 1                              | None                                 | None                  | None           | None                    |
| 7            | 1                              | Moderate progestational              | Hyperes-<br>trogenic  | None           | Moderate progestational |
| 8            | 1                              | None                                 |                       |                |                         |
| 9            | 1                              | Progestational                       | None                  | Progestational |                         |
|              | 2                              | Progestational                       | Persistent estrogenic |                |                         |
|              | 3                              | Moderate progestational              |                       |                |                         |
| 10           | 1                              | Progestational                       |                       |                |                         |
|              | 2                              | None                                 | Progestational        |                |                         |
| 12           | 1                              | None                                 |                       |                |                         |
| 13           | 1                              | None                                 | None                  | None           |                         |

with the course of therapy 8 days later. Estrogen withdrawal bleeding followed after 5 days.

*Effect upon duration and amount of uterine bleeding.* There was a tendency for changes in the duration of bleeding during therapy to parallel the alteration in the length of the cycle. Those patients who had con-

sistently shortened cycles experienced shorter episodes of bleeding, while those who had lengthened cycles had notably longer bleeding phases. Those patients in whom alterations in the length of the cycle were variable experienced no significant changes in the duration of bleeding. These tendencies disappear, however, when averages of the duration of bleeding for the whole group before, during and after therapy are considered. These averages were 5.8 days, 5.0 days and 6.8 days, respectively.

It was observed that the episodes of bleeding which followed the first cycle after cessation of therapy generally were longer than the average duration prior to treatment. In subsequent cycles, however, bleeding phases of normal length often recurred.

The influence of therapy upon the amount of uterine bleeding was of the same order as that upon the duration of bleeding. The patients who experienced shortened cycles as a result of therapy reported a decrease in the number of sanitary pads required. An increase in the number of pads required was reported by those patients who had lengthened cycles. No significant findings were encountered in patients who experienced no characteristic alterations of menstrual flow. The average number of well saturated pads

days. In the case of the only patient in whom therapy lasted from the 5th to the 24th day of the cycle, the time between cessation of therapy and the onset of bleeding averaged 2.8 days. The average length of the cycle of this patient prior to treatment was 25.4 days.

**Effect upon urinary excretion of sodium pregnanediol glucuronide.** Determinations of the pregnanediol complex levels were made on the urine of 6 patients during a total of 6 cycles prior to therapy, and during

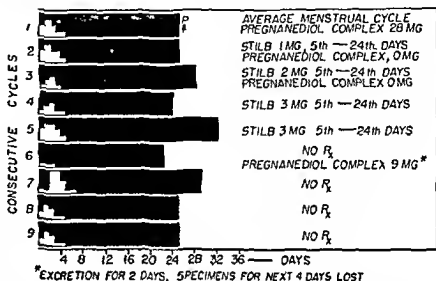


FIG 2 EFFECTS OF DIETHYLSTILBESTROL (Stilb) on duration of bleeding cycles and pregnanediol excretion of patient 13. Episodes of bleeding are represented for each cycle at the left of the graph.

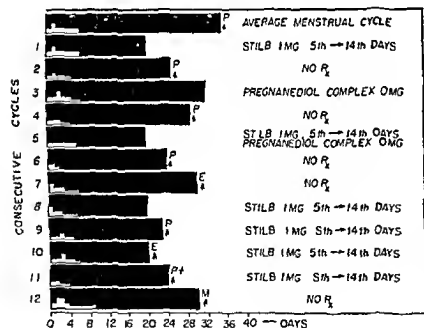


FIG 1 EFFECTS OF DIETHYLSTILBESTROL (Stilb) on duration of bleeding cycles endometrial responses (P and P+, progesterone and estrogenic) and pregnanediol excretion of patient 9. Episodes of bleeding are represented for each cycle at the left of the graph.

used by the group as a whole prior to, during and after therapy were 13, 10 and 13, respectively.

**Effects upon withdrawal bleeding time.** The criterion employed for the definition of withdrawal bleeding was the occurrence of an episode of bleeding within a few days after cessation of therapy and considerably in advance of the expected date of bleeding. In 14 cycles of 7 treated patients the withdrawal bleeding time averaged 6 days. The range was from 2 to 8 days. The length of these cycles averaged 19.5

a total of 7 cycles in these patients during treatment. Only 2 patients excreted the complex prior to therapy, 28 and 31 mg, respectively, were recovered. No pregnanediol complex was recovered in any of the patients during treatment. Endometrial studies were made at the onset of bleeding in 3 cycles of 3 of these patients during treatment. The endometria were estrogenic in nature.

The number of determinations of the pregnanediol complex averaged 13 per patient prior to therapy, and 19 per patient during treatment.

**Untoward effects.** No significant untoward effects of therapy were observed or reported by the patients.

#### DISCUSSION

The contraphysiologic employment of moderately small doses of the non hormonal estrogen, diethylstilbestrol, in women with normal ovarian function produced definite effects upon the menstrual cycle. These effects were manifested in the various elements characteristic of the menstrual cycle, i.e., the status of the endometrium at the onset of bleeding, the length of the cycle and duration and character of the flowing.

The occurrence of depressions of corpus luteum function in a number of instances was indicated by the preponderance (67%) of specimens of estrogenic endometria over progesterone ones (33%) during therapy. This effect often occurred during the first cycles of treatment. Of 8 endometrial samples taken

at this time, 5 were estrogenic and 3 were progestational in nature.

Diethylstilbestrol therapy was associated with disturbances in the cyclic nature of bleeding in all but one patient. These alterations in the amount of bleeding were not directly proportional to alterations in duration of bleeding, but represented an actual increase or decrease of the flow.

Variations in endometrial response and in alteration of the bleeding cycles of patients, and, in several instances, of the same individual, on the same dosage, are worthy of note. These differences may be explained on the basis of individual ovarian capacity and the varying tolerance of these patients to an exogenous synthetic non-hormonal estrogen.

It is apparent from the data presented that the effects of diethylstilbestrol on the menstrual cycle, which were observed during treatment, are not cumulative. No instances of prolonged persistent depression of ovarian function were encountered. Progestational endometrium was found in each of 5 instances wherein endometrial samples were obtained at the end of the first cycle which occurred subsequent to the cessation of therapy, despite the fact that some of these patients had received therapy during 2 to 4 antecedent cycles. The occurrence of progestational endometrium in 80 per cent of the specimens obtained during cycles following therapy, the recurrence of cyclic bleeding and the return of flow to one of normal duration and amount following cessation of therapy, are additional evidence that, in the dosages and manner of administration employed, diethylstilbestrol has no lasting undesirable effects.

These findings, however, do not warrant any statement with regard to the ultimate results that follow protracted therapy with larger doses of diethylstilbestrol.

#### SUMMARY

Moderately small doses of diethylstilbestrol were used contraphysiologically in 13 women who had normal ovarian function. Depression of corpus luteum function during therapy was indicated by bleeding from an estrogenic endometrium in two-thirds of the cycles during which the endometrium was sampled. The failure to recover sodium pregnanediol glucuronide from the urine of 6 patients during therapy was taken as further evidence for depression of corpus luteum function.

Marked alterations in the menstrual cycle occurred with regard to length of the cycle and to duration and amount of bleeding.

The effects of diethylstilbestrol apparently are not cumulative when it is used in therapeutic schedules comparable to those reported. No prolonged, undesirable effects were noted. Progestational endometrium was encountered in all biopsies which were secured at the end of the first cycle which followed cessation of therapy. These findings do not warrant any statement regarding results that might follow the prolonged use of diethylstilbestrol in larger doses.

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# Effects of Desoxycorticosterone Acetate on 17-Ketosteroid and Pregnanediol Excretions<sup>1</sup>

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IN AN EARLIER REPORT, by members of our group, which considered the progesterone like effect of desoxycorticosterone acetate administered intramuscularly to women, it was observed that no evidence existed that desoxycorticosterone acetate was metabolized into androgenic substances (1). More recently, additional data have been gathered which are relative to this point. Determinations for 17 ketosteroids were made on the urine of 2 patients with Addison's disease who were being treated with desoxycorticosterone acetate.<sup>2</sup> The results of these led to further studies of the administration of this substance to normal individuals. The present communication deals with these studies.

## METHODS

The individuals studied were divided into 3 groups as follows: group 1, patients with Addison's disease, group 2, women with intercurrent ovarian failure associated with the absence of uterine bleeding, group 3, normal individuals.

Group 1 consisted of 2 patients, a woman aged 32 years and a man aged 39 years, who were hospitalized for an evaluation of presumed Addison's disease. Studies of daily 24 hour urine specimens were made on both patients during hospitalization. These were continued on the woman after her discharge from the hospital and were resumed upon her return for additional therapy. Determinations of urinary 17 ketosteroids were made in the case of both patients prior to and during therapy. The urinary excretion of sodium

pregnanediol glucuronide was studied only in the woman and after initiation of treatment.

Group 2 was comprised of 5 women who had intercurrent ovarian failure which was associated with the absence of uterine bleeding for periods ranging from 3 to 9 months. The average age of these patients was 25 years. Urinary levels of 17 ketosteroids and of the pregnanediol complex were determined prior to and during therapy. The therapeutic schedule employed was essentially the following: Estrone (10,000 i.u.) or estradiol benzoate (2000 R.U.) was given intramuscularly daily for 14 consecutive days, desoxycorticosterone acetate (5 mg) and either estrone (10,000 i.u.) or estriol glucuronide (1800 oral units) was given daily the next 14 days (therapy being discontinued, however, if bleeding began). One patient received two cycles of this therapy. The total dosage of desoxycorticosterone acetate ranged from 35 mg to 60 mg per cycle with an average of 47.5 mg.

Group 3 consisted of 5 healthy individuals who volunteered for this investigation. In the group were 3 men whose ages averaged 26 years and 2 women whose average age was 26 years. The women each received desoxycorticosterone acetate intramuscularly, 5 mg daily for 5 days, beginning on the 12th day of the menstrual cycle. The men each received intramuscularly 10 mg of desoxycorticosterone acetate daily for 5 days. Two of the men each had 2 courses of treatment. Consecutive 24 hour urine specimens were collected, beginning 4 days prior to initiation of therapy and ending from 4 to 11 days following the last injection. Levels of 17 ketosteroids were established on all individuals. The pregnanediol complex excretion was studied only in the males. The average daily titers of 17 ketosteroids were established as follows: a), prior to treatment, b), during

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<sup>1</sup> Part of the expenses of these studies was defrayed by grants to one of us (E.C.H.) from the Research Council of Duke University and from Schering Corporation, Bloomfield, N. J.

\* Deceased April 10, 1942.

<sup>2</sup> Cortate, supplied by Schering Corporation, Bloomfield, N. J.

treatment and c), following treatment. The term 'during treatment' was defined to include the 5 days of treatment and the first 2 days following cessation of therapy.

The estimation of 17-ketosteroids was made colorimetrically by the method of Oesting (2, 3),

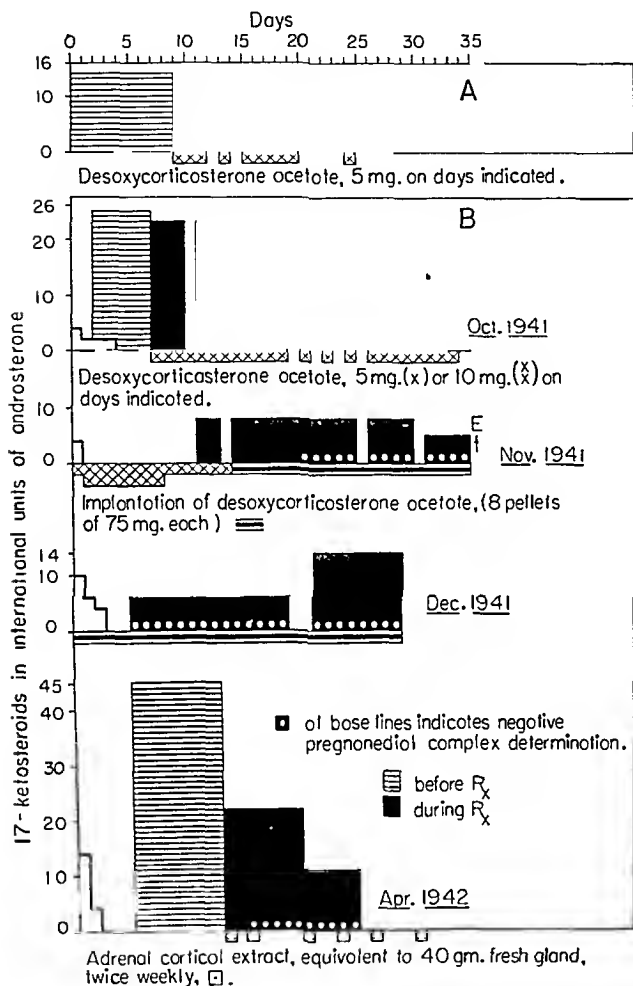


FIG. 1. A. Patient F. N., ♂ ADDISON'S DISEASE. Levels of urinary 17-ketosteroids associated with desoxycorticosterone therapy. B. Patient M. T., ♀ ADDISON'S DISEASE. Levels of urinary 17-ketosteroids and sodium pregnanediol glucuronide associated with therapy consisting of desoxycorticosterone acetate and adrenal cortical extract. Episodes of uterine bleeding are represented at the beginning of each cycle by outlined blocks. E signifies persistent estrogenic endometrium judged by endometrial biopsy.

after urinary extraction by the method of Cuyler and Baptist (4). Determinations of sodium pregnanediol glucuronide were made by Venning's method (5).

#### DATA

**Patients with Addison's disease.** The data on these patients are presented in the following short summaries and in figure 1.

**Patient F. N.,** a 39-year-old white married male was referred to the Endocrine Division for an evaluation of symptoms and consideration of therapy. Response

to therapy with desoxycorticosterone acetate was unfavorable. The patient was discharged and placed on a high sodium chloride intake. Figure 1, A, relates details of treatment with desoxycorticosterone acetate and daily excretion levels of 17-ketosteroids averaged by weeks.

**Patient M. T.,** a 32-year-old, white housewife, para 3, 0, 3, was referred to the Endocrine Division for an evaluation of symptoms and recommendations as to therapy. Trials of treatment with an increased salt intake and varying doses of desoxycorticosterone acetate were made. Eight pellets of 75 mg. each of this substance were implanted subcutaneously in the right subscapular region. Progress in the hospital after implantation of pellets was satisfactory. For a few weeks following discharge, the patient showed evidences of over-treatment. Five months after initial treatment, further therapy was required. This consisted of intramuscular administration of adrenal cortical extract.<sup>3</sup> Details of therapy and related urinary levels of 17-ketosteroids and the pregnanediol complex are shown in figure 1, B. The daily 17-ketosteroid excretion levels are reported in terms of weekly averages. This patient had had infrequent uterine bleeding prior to treatment. Under therapy, periodic bleeding was re-established.

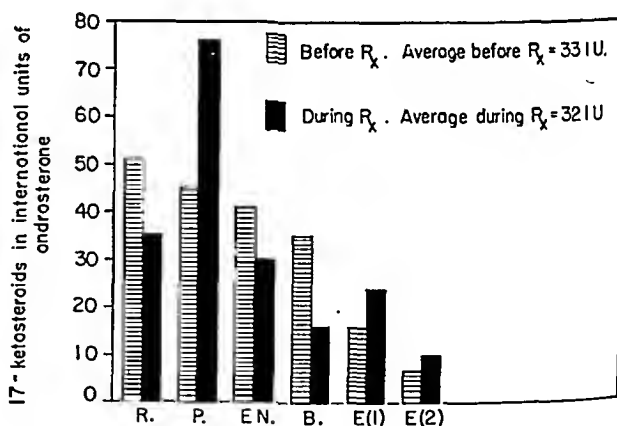


FIG. 2. LEVELS OF URINARY 17-KETOSTEROIDS before and during desoxycorticosterone acetate therapy in 5 women with intercurrent ovarian failure. Patient E had 2 series of study.

**Patients with intercurrent ovarian failure.** None of these 5 patients excreted sodium pregnanediol glucuronide prior to treatment. During therapy, the pregnanediol complex was recovered from the urine of 3 patients in total amounts of 3, 6 and 9 mg., respectively. Uterine bleeding followed treatment in one of these 3 patients. Endometrial studies in 2 of these 3 patients showed persistent estrogenic endometria. The averaged daily excretion levels of urinary

<sup>3</sup> The adrenal cortical extract was prepared by The Upjohn Co., of Kalamazoo, Mich.

17 ketosteroids prior to and during therapy are presented in figure 2

**Normal individuals** No pregnanediol complex was recovered from the urine of the 3 males studied. The averaged daily levels of 17 ketosteroid excretion before, during and following treatment are presented in figure 3. Therapy had no effect upon the regularity of uterine bleeding in the two female patients.

#### DISCUSSION

**17-Ketosteroid levels.** A depression of urinary 17-ketosteroid levels followed institution of therapy with desoxycorticosterone acetate in each of the two patients with Addison's disease. In the female, depressed values continued during 3 bleeding cycles. This finding is not in agreement with those of the workers (6) who found a very slight increase in 17-ketosteroid values during administration of desoxycorticosterone acetate of comparable dosage to women with Addison's disease. This difference may be accounted for in the status of the patients, or possibly in the number of determinations made in establishing levels before and during therapy.

Our two patients were not in a particularly grave state of adrenal cortical insufficiency. This is reflected in the fact that one patient (F. N.) could be maintained on increased salt intake alone and that, in the replacement therapy in the second patient the maintenance dosage was finally found to be rather small. The pretreatment levels of urinary 17 ketosteroids in these patients were of the same order as reported by others in association with Addison's disease (6, 7).

The depression in 17 ketosteroid levels in the case of the female, figure 1, B, occurred during intramuscular administration of desoxycorticosterone acetate, persisted for a time during therapy by pellet implantation and was observed also after the administration intramuscularly of an adrenal extract, in amounts equivalent to 40 gm of fresh tissue, twice weekly. This amount (40 gm) corresponds roughly to 0.15 mg of desoxycorticosterone acetate (8, 9). The increased 17 ketosteroid level of the female patient upon her second hospital visit may be related to the exhaustion of the implanted pellets.

It is apparent from figures 2 and 3 that no consistent alterations of 17 ketosteroid levels follow administration of desoxycorticosterone acetate to patients with intercurrent ovarian failure or to normal individuals. In the cases of these groups of individuals, the data do not offer conclusive evidence of depressing effects upon the adrenal cortex. Since desoxycorticosterone acetate has been shown to have an estrogenic action in women (10) and since our group found decreased 17 ketosteroid levels in women during estrogenic therapy (11), it was expected that decreased levels might follow administra-

tion of desoxycorticosterone acetate. However, the results were equivocal in the two normal women there was virtually no alteration of 17 ketosteroid levels during therapy, while in the case of women with intercurrent ovarian failure, 3 patients had decreased levels and 2 patients had increased levels during treatment.

It cannot be concluded from the data presented that desoxycorticosterone acetate, after intramuscular administration or pellet implantation, is altered to

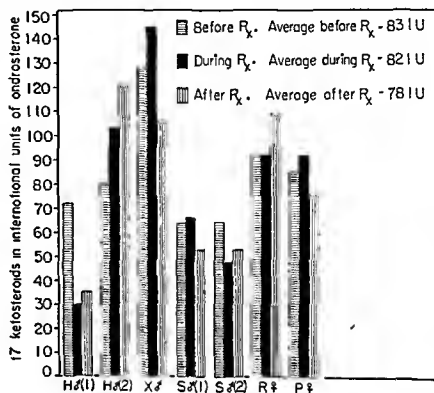


FIG. 3 LEVELS OF URINARY 17 KETOSTEROIDS\* before, during and after desoxycorticosterone acetate therapy in 5 normal individuals\* 3 men and 2 women. Two of the men (H and S) had a series of study

products which are recoverable by our procedure for extracting urinary 17 ketosteroids

With regard to the alteration in 17-ketosteroid level during therapy with desoxycorticosterone acetate, no constant change was observed in individuals who had normal adrenal function. On the other hand, evidence is presented (fig. 1, B) that in Addison's disease this level varies inversely with dosage and extent of therapy. This correlation may prove to be an indicator of pellet exhaustion before clinical symptoms and signs re appear.

**Excretion of sodium pregnanediol glucuronide** No pregnanediol complex was recovered from the urine of the female patient with Addison's disease during treatment with desoxycorticosterone acetate or with adrenal cortical extract. Only small amounts of the complex were recovered during therapy from the urine of the patients with intercurrent ovarian failure. The normal males excreted no urinary pregnanediol complex during therapy. We do not regard this last finding as conflicting necessarily with a previous report by our group (12) which described

the recovery of sodium pregnanediol glucuronide from the urine of a healthy male during the administration of desoxycorticosterone acetate. Marked variations exist in the ability of different males to metabolize progesterone administered intramuscularly (13) and to excrete ingested sodium pregnanediol glucuronide (14). However, the difference between the results on the males in the present study and the results reported previously may be one of age. The ages of the normal males in this study ranged from 21 to 31 years. The age of the male reported previously (12) was 39 years.

#### SUMMARY

The urinary excretion of 17-ketosteroids and sodium pregnanediol glucuronide has been studied during the treatment of 2 patients with Addison's disease, 5 women with intercurrent ovarian failure and 5 normal individuals (3 males, 2 females) with desoxycorticosterone acetate.

No constant alterations in the urinary levels of 17-ketosteroids were observed during the administration of desoxycorticosterone acetate to normal individuals of either sex, or to women with intercurrent ovarian failure. Therapy with desoxycorticosterone acetate or adrenal cortical extract in Addison's disease was

associated with a decrease in 17-ketosteroid levels.

No evidence was encountered that any of the desoxycorticosterone acetate given was metabolized into sodium pregnanediol glucuronide.

The authors wish to express their appreciation to those individuals who volunteered their services for these studies.

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# Progesterone Therapy and Progestin Metabolism in Abortion<sup>1</sup>

## [Progesterone and Abortion]

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THE COUNCIL ON PHARMACY AND CHEMISTRY of the American Medical Association recently stated "It is indeed difficult to conclude from the available data whether or not progesterone or active corpus luteum extracts are of value in the treatment of habitual and threatened abortion" (1) The accurate evaluation of therapy, of necessity, must remain difficult until we have a better understanding of the etiologic factors in abortion

Diagnosis of threatened abortion has been rendered uncertain by the fact that biologically active progestin is identified in human tissues and fluids in only small quantities by the present methods of bioassay. Some of the more recent and more sensitive of these methods have not been applied to clinical studies

Venning's (2) method for the determination of pregnanediol, an excretion product of progestin metabolism, aroused much enthusiasm. It was hoped that, at last, there was a diagnostic implement by which significant alterations in intrinsic progestin levels might be determined. The matter of raising the lower of these levels was deemed to be practical since crystalline progesterone was available.

Five years now have elapsed since Venning's method was described. During the last four years in our laboratory a total of 7142 twenty four hour urine specimens of 235 women has been examined for pregnanediol. A total of 788 twenty four hour urine specimens has been studied on 14 obstetric patients.

This communication evaluates progestin therapy with reference to its general effectiveness in warding off abortion or miscarriage and to its relationship to levels of corpus luteum and chorio placental function in pregnancy.

### METHODS

Each patient included in this report received complete gynecologic and endocrine surveys which comprised thorough general physical examinations, anthropometric measurements, basal metabolic determinations, roentgenograms of the sella turcica, and other special examinations when these were deemed indicated.

The diagnosis of pregnancy was substantiated by hormone tests when the duration of pregnancy prevented positive diagnosis by pelvic examinations.

In some of these cases consecutive 24-hour specimens of urine were collected for sodium pregnanediol glucuronide determinations. The Venning method was followed. Our results are reported as daily excretions, averaged by weeks, and in terms of milligrams of sodium pregnanediol glucuronide.

### THERAPEUTIC REGIMEN

No one regime has been followed in our therapy to prevent abortion. The common element in all regimens has been progestin or crystalline progesterone.<sup>2</sup> The weekly dosage ranged from 3 to 140 mg.

We have employed also many of the time honored methods, including bed rest when symptoms were present, decreased activity at all times and abstinence from intercourse.

Those patients with histories of recurrent abortions were treated as soon as the diagnosis of pregnancy was made or when the patients first came under our care. The amount of progesterone employed varied from 10 mg daily to 5 mg twice weekly. Five patients received anhydrohydroxyprogesterone<sup>3</sup> orally in daily amounts ranging from 20 to 60 mg. As a rule,

<sup>1</sup>Received for publication May 11, 1942.

<sup>2</sup>Part of the expenses of these studies was defrayed by grants to one of us (E.C.H.) from the Research Council of Duke Hospital from Schering Corp., Bloomfield, N. J., and from Ayerst McKenna and Harrison, Montreal, Canada.

<sup>3</sup>Progesterone was supplied by Eli Lilly & Company, Indianapolis, Ind.

Corr., N. W. Univ., N. J.



TABLE 1. PERTINENT CLINICAL DATA OF PATIENTS WITH HISTORIES OF RECURRENT ABORTIONS

| Case No. | Parity  | Treatment Formula <sup>1</sup>                    | Week Progesterone Therapy Begun | Week Symptoms Occurred | Week Progesterone Therapy Discontinued | Week Pregnancy Terminated         |
|----------|---------|---|---------------------------------|------------------------|--|-----------------------------------|
| 1        | 3-3-0   | Progesterone and thyroid                          | 16                              |                        | 36                                     | 40                                |
| 2        | 4-4-0   | Progesterone and thyroid                          | 5                               |                        | 33                                     | 33                                |
| 3        | 2-2-0   | Progest.+ch. gonad.+est. gluc.+thyr.+anhydox-prog | 6                               |                        | 33                                     | 40                                |
| 4        | 8-7-0   | Anhydox-prog.+thyr.                               | 18                              |                        | 41                                     | 41                                |
| 5        | 5-4-1   | Progest.+ch. gonad.+est. gluc.                    | 6                               |                        | R <sub>x</sub> continues               | Undelivered, patient in 34th week |
| 6        | 3-3-0   | Progest.+ch. gonad.+est gluc.+thyr.               | 5                               |                        | R <sub>x</sub> continues               | Undelivered; patient in 33rd week |
| 7        | 2-2-0   | Progest.+est. gluc.+thyr.                         | 5                               |                        | R <sub>x</sub> continues               | Undelivered, patient in 32nd week |
| 8        | 5-5-0   | Anhydox-prog.+est. gluc.+thyr.                    | 20                              |                        | 26                                     | Undelivered; patient in 32nd week |
| 9        | 10-10-0 | Anhydox-prog.+thyr.                               | 8                               | 30                     | 30                                     | 30 (neonatal death)               |
| 10       | 6-5-1   | Progest.+ch. gonad.+est. gluc.                    | 11                              | 29                     | 29                                     | 29 (stillbirth)                   |
| 11       | 4-4-0   | Progest.+est. gluc.+thyr.                         | 10                              | 13                     | 13                                     | 13                                |
| 12       | 3-3-0   | Progest.+ch. gonad.+est. gluc.+thyr.              | 6                               | 24                     | 27                                     | 25                                |
| 13       | 3-3-0   | Progest.+ch. gonad.                               | 6                               | 31                     | 31                                     | 31                                |
| 14       | 8-8-0   | Progest.+ch. gonad.+est. gluc.                    | 15                              | 19                     | 19                                     | 19                                |
| 15       | 3-3-0   | Progest.+ch. gonad.                               | 5                               | 12                     | 12                                     | 12                                |
| 16       | 4-4-0   | Anhydox-progest.+est. gluc.+thyr.                 | 12                              | 15                     | 15                                     | 15                                |

<sup>1</sup> Treatment Formula: Progest., progesterone, Anhydox-prog., anhydrohydroxyprogesterone; Est. gluc., estriol glucuronide, Ch. gonad., chorionic gonadotropin; Thyr., thyroid substance.

TABLE 2. PERTINENT CLINICAL DATA OF PATIENTS WITH HISTORIES OF THREATENING ABORTION

| Case No. | Parity | Treatment Formula <sup>1</sup>                          | Week Progesterone Therapy Begun | Week Symptoms Occurred | Week Progesterone Therapy Discontinued | Week Pregnancy Terminated         |
|----------|--------|---|---------------------------------|------------------------|--|-----------------------------------|
| 17       | 1-1-0  | Progest.+ch. gonad.+est. gluc.                          | 7                               | 7                      | 36                                     | 40                                |
| 18       | 2-0-2  | Progest.+est. gluc.+anhydox-prog.                       | 23                              | 23                     | 28                                     | 38                                |
| 19       | 0-0-0  | Anhydox-prog.+thyr.                                     | 11                              | 11                     | 33                                     | 38                                |
| 20       | 1-0-1  | Progest.+ch. gonad.+est. gluc.+thyr.                    | 19                              | 17                     | 28                                     | 40                                |
| 21       | 2-0-2  | Progest.+anhydox-prog.+thyr.                            | 23                              | 18                     | 30                                     | 41                                |
| 22       | 2-2-0  | Progest.+est. gluc.+thyr.                               | 25                              | 23                     | 38                                     | 41                                |
| 23       | 0-0-0  | Progest.+est. gluc.+anhydox-prog.                       | 17                              | 16                     | 22                                     | 38                                |
| 24       | 0-0-0  | Progest.+est. gluc.                                     | 23                              | 23                     | 24                                     | 31                                |
| 25       | 0-0-0  | Progest.+ch. gonad.+est. gluc.+anhydox-prog.+thyr.      | 13                              | 13                     | 37                                     | 40                                |
| 26       | 0-0-0  | Anhydox-prog.+thyr.                                     | 15                              | 14                     | 23                                     | 39                                |
| 27       | 0-0-0  | Progest.+ch. gonad.+est. gluc.                          | 13                              | 12                     | 27                                     | 35                                |
| 28       | 3-2-0  | Progest.+est. gluc.                                     | 20                              | 20                     | 25                                     | 38                                |
| 29       | 0-0-0  | Progest.+thyr.  | 17                              | 17                     | 17                                     | 40                                |
| 30       | 1-1-0  | Progest.+est. gluc.                                     | 11                              | 10                     | R <sub>x</sub> continues               | Undelivered; patient in 33rd week |
| 31       | 0-0-0  | Progest.+ch. gonad.+estradiol benz.+anhydox-prog.+thyr. | 13                              | 7                      | R <sub>x</sub> continues               | Undelivered, patient in 20th week |
| 32       | 0-0-0  | Progest.+est. gluc.+anhydox-prog.+thyr.                 | 19                              | 19                     | R <sub>x</sub> continues               | Undelivered, patient in 34th week |
| 33       | 1-0-1  | Anhydox-prog.+est. gluc.+thyr.                          | 8                               | 8                      | R <sub>x</sub> continues               | Undelivered; patient in 26th week |
| 34       | 1-1-0  | Progest.+ch. gonad.+est. gluc.+thyr.                    | 9                               | 9                      | 12                                     | 12                                |
| 35       | 1-1-0  | Progest.+ch. gonad.+est. gluc.                          | 6                               | 5                      | 13                                     | 13                                |
| 36       | 5-5-0  | Progest.+thyr.  | 8                               | 7                      | 13                                     | 13                                |
| 37       | 0-0-0  | Progest.+ch. gonad.+est. gluc.                          | 11                              | 8                      | 14                                     | Missed abortion                   |
| 38       | 4-3-1  | Progest.+est. gluc.                                     | 15                              | 15                     | 18                                     | 18                                |
| 39       | 2-1-1  | Progest.+ch. gonad.+est. gluc.                          | 9                               | 8                      | 12                                     | 12                                |
| 40       | 0-0-0  | Progest.+ch. gonad.+est. gluc.                          | 11                              | 11                     | 12                                     | 12                                |
| 41       | 0-0-0  | Progest.+ch. gonad.+est. gluc.                          | 12                              | 12                     | 13                                     | 13                                |
| 42       | 1-1-0  | Progest.+est. gluc.                                     | 14                              | 5                      | 17                                     | 17                                |
| 43       | 1-0-1  | Progest.+ch. gonad.+est. gluc.                          | 7                               | 7                      | 8                                      | 8                                 |
| 44       | 0-0-0  | Progest.+est. gluc.                                     | 5                               | 5                      | 6                                      | 6                                 |
| 45       | 2-2-0  | Progesterone  | 7                               | 7                      | 8                                      | 8                                 |
| 46       | 5-2-3  | Progesterone  | 10                              | 7                      | 10                                     | 23                                |

<sup>1</sup> See footnote, table 1; Estradiol benz., estradiol benzoate.

TABLE 3. PERTINENT CLINICAL DATA OF PATIENTS INCLUDED IN THE PROGNOSTICATED ABORTION GROUP

| Case No. | Parity | Treatment Formula <sup>1</sup>                 | Week Progesterone Therapy Begun | Week Symptoms Occurred | Week Progesterone Therapy Discontinued | Week Pregnancy Terminated         |
|----------|--------|--|---------------------------------|------------------------|--|-----------------------------------|
| 47       | 0-0-0  | Progesterone + ch. gonad. + est. gluc. + thyr. | 7                               | 9 through 11           | 36                                     | 40                                |
| 48       | 0-0-0  | Progesterone                                   | 7                               |                        | 20                                     | 40                                |
| 49       | 1-1-0  | Progesterone + est. gluc.                      | 10                              |                        | 33                                     | 39                                |
| 50       | 0-0-0  | Anhydros-prog. + est. gluc. + thyr.            | 12                              |                        | 32                                     | 39                                |
| 51       | 0-0-0  | Progesterone + ch. gonad. + est. gluc. + thyr. | 7                               |                        | 34                                     | 40                                |
| 52       | 0-0-0  | Progesterone + ch. gonad. + est. gluc. + thyr. | 7                               |                        | R continues                            | Undelivered; patient in 30th week |
| 53       | 0-0-0  | Progesterone + est. gluc. + thyr.              | 7                               | 7                      | 8                                      | 8                                 |
| 54       | 1-1-0  | Progesterone + corp. lut. ext. + thyr.         | 10                              | 17                     | 17                                     | 17                                |

<sup>1</sup> See footnote, table 1; Corp. lut. ext., corpus luteum extract.

dosage was reduced as pregnancy progressed. Usually therapy was discontinued about the 33rd to the 36th week. In the majority of instances estiol glucuronide<sup>4</sup>

chorionic gonadotropin<sup>5</sup> in amounts ranging from 300 to 600 i.u. was given every day or every other day until the 16th to 18th week. When it seemed to be

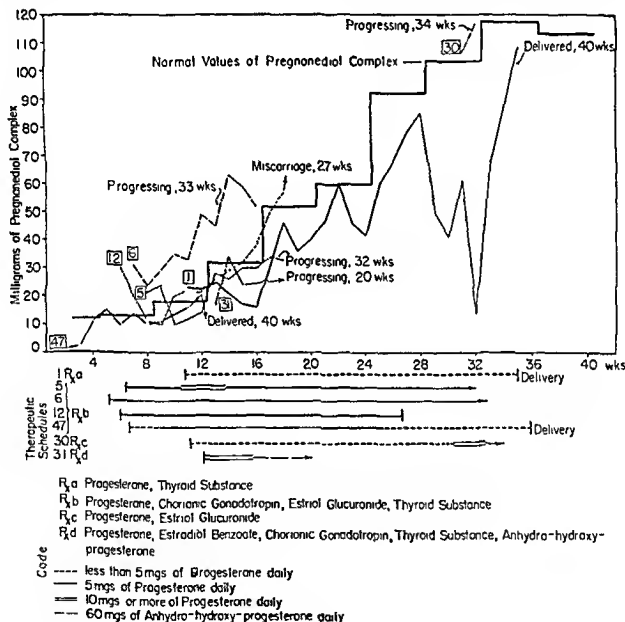


FIG. 1. URINARY EXCRETION OF PREGNEDIOL COMPLEX, therapy and clinical course of patients 12, 51, 52, 30, 31, 47. The pregnancies of 6 of these 7 progressed normally or went to term. The values for pregnediol complex are in milligrams.

was given orally in daily doses ranging from 480 to 960 day-oral units. In about one-half of the patients,

<sup>4</sup> Estiol glucuronide (Emmenin), supplied by Ayerst, McKenna & Harrison, Montreal, Canada.

indicated, thyroid substance was given to full clinical tolerance during the course of pregnancy.

<sup>5</sup> APL, supplied by Ayerst, McKenna & Harrison, Montreal, Canada.



## DISCUSSION

The literature on progesterone therapy in recurrent and threatening abortion has been reviewed recently by Kotz, Parker and Kaufman (10). In this report there was 79 per cent success in a collected group of 273 patients with histories of recurrent abortions, and in a total of 69 patients with histories of threatening abortion, therapy was successful in 81 per cent. Kotz et al reported treatment of 42 patients, with histories of recurrent abortion or ovarian sterility, with success in 88 per cent of the cases. In their threatening abortion group of 184 pa-

term or are progressing satisfactorily. Pregnancies were maintained in 48 per cent of the 23 patients who received chorionic gonadotropin. Seventy two per cent of the 29 patients who received thyroid substance went to term. From this analysis, it appears that neither estriol glucuronide nor chorionic gonadotropin is of therapeutic value. Thyroid substance does seem to enhance the efficacy of treatment when hypometabolism exists.

It is accepted generally that most spontaneous abortions occur about the time the second and third menses are missed. Theoretically, one might expect

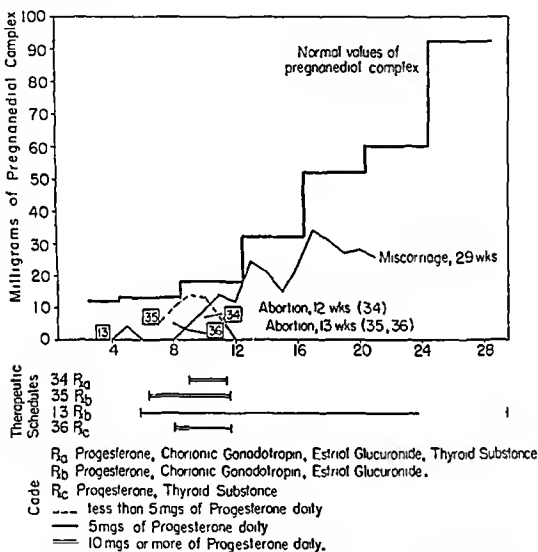


FIG 3. URINARY EXCRETION OF PREGNANEOL COMPLEX therapy and clinical course of patients 13, 34, 35, 36. All of these patients aborted or miscarried. See figure 1 for explanation of pregnaneol complex values. The values for these 4 patients were initially depressed.

tients, 139 were treated with progesterone and 45 received no progesterone. Forty six per cent of the treated patients went to term and 49 per cent of those who received no progesterone went to term.

Our results are poorer than most of those reported in the literature. Our successes were 57 per cent in the threatening abortion group, 50 per cent in the recurrent abortion group and 75 per cent in the prognosticated abortion group.

Does the use of estriol glucuronide, chorionic gonadotropin or thyroid substance alter the efficiency of progesterone therapy? The total success in the 54 patients was 57 per cent. Sixty per cent of the 38 patients who received estriol glucuronide went to

term. The earlier the initiation of therapy in the patients treated prophylactically and the later the onset of symptoms in the patients threatening abortion, the better would be the prognosis. The apparent exception to this generalization is the patient who has passed through the time of maximum danger and who subsequently receives prophylactic treatment. Every patient in the prognosticated abortion group received therapy prior to the end of the 12th week. The maintenance of pregnancy in those patients of the recurrent abortion group who were placed on therapy prior to the end of the 12th week was 42 per cent (5 of 12) and was 75 per cent (3 of 4) in those patients placed on therapy after the 12th week. We

had 92 per cent (11 of 12) success in treating threatening abortion when symptoms started after the 12th week and 33 per cent (6 of 18) success when symptoms began before the end of the 12th week. The implications are obvious and these may explain partially the marked differences in our results from those reported in the literature.

Oral anhydrohydroxyprogesterone was used in 15 patients, initially in 8 patients and following therapy by injection in 7 instances. In no patient were there any symptoms of threatening abortion associated with the change from the injection to the oral form of therapy. It seemed that oral therapy was as efficacious as injection therapy. The dosage ratio between injected progesterone and oral anhydrohydroxyprogesterone has been assumed to be about 1 to 10.

Justification for the inclusion of the so-called prognosticated abortion group in this report seems obvious (11). An objective diagnosis of deficient ovarian function was made prior to pregnancy and there is reason to believe that the fertile state was brought about by therapeutic measures. The predication of a likely return of a state of ovarian deficiency during pregnancy seems warranted. The fact that 3 patients of this group who did have symptoms of threatening abortion (2 aborted) had these symptoms early in pregnancy tends to confirm this predication.

The urinary level of sodium pregnanediol glucuronide appears to be of prognostic significance in the pregnant woman (12). Four patients, in whom the pregnanediol-complex values were initially and continually low, aborted or miscarried. Three patients, in whom pregnanediol values were normal but were followed by zero or near zero values, aborted or miscarried within a few days after this sharp decline in the excretion of the pregnanediol-complex. Six of 7 patients with continually normal values went to term. The one patient in this latter group who did not go to term had premature rupture of the membranes during the 22nd week and miscarried during the 25th week.

The fact that the level of sodium pregnanediol glucuronide excretion could not be raised by the therapeutic use of progesterone (13) makes it impossible to use this method as a guide to therapy. Thus one of the sanguine expectations for the application of the method has not been established.

All obstetric patients studied by us have excreted some sodium pregnanediol glucuronide (14). Wilson, Randall and Osterberg (15) believe that the excretion of over 10 mg. of pregnanediol-complex is diagnostic of pregnancy. In 3 patients (cases 36, 34 and 13), the diagnosis of pregnancy would not have been established by these criteria as late as the 8th, 10th, 12th

weeks respectively. Buxton (16) believes that the pregnanediol method has value in establishing a negative diagnosis. He states that, 'no pregnancy cases have been observed here or reported elsewhere, which had negative pregnanediol determinations.' One patient (case 13) is an exception, for zero levels were found during the 4th, 6th, 7th and 8th weeks of pregnancy. It is difficult for us to justify the use of the pregnanediol method to establish or rule out a diagnosis of pregnancy.

#### SUMMARY

The results of therapy for the prevention of abortion, progesterone being the common therapeutic element, is reported in 54 patients. Sixteen of these patients had histories of recurrent abortion; pregnancy was maintained in 50%. Thirty had histories of threatening abortion; pregnancy was maintained in 57 per cent. Eight had pre-gestational diagnoses of ovarian failure; pregnancy was maintained in 75 per cent of these.

Thyroid substance was an important adjunct, if not the major therapeutic factor, in patients with hypometabolism. The earlier that prophylactic therapy is started and the later the appearance of symptoms which necessitate active therapy, the better the results of therapy. Oral anhydrohydroxyprogesterone was apparently as efficient as injected progesterone.

The sodium pregnanediol glucuronide excretion values of 14 patients were studied. Six of 7 patients who excreted normal levels of pregnanediol went to term. Four patients who had initially and continually low levels aborted or miscarried. Three patients who had normal levels followed by zero or near zero values aborted or miscarried within a few days after the sudden drop in the pregnanediol excreted.

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# Treatment of Prepuberal Vulvovaginitis with Diethylstilbestrol<sup>1</sup>

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IN 1940 (1) we presented a preliminary report of a series of 25 cases of infant vulvovaginitis treated by means of diethylstilbestrol administered orally. We have continued this investigation until the present and are able to present 124 cases so treated for critical review.

The greater majority of these cases have been followed more than one year, none less than three months and some more than two years.

## MATERIAL

As in the previous report the material consists of cases of vulvovaginitis from the Departments of Pediatrics and Gynecology of Hutchinson Memorial Clinic, Charity Hospital Clinic, Touro Infirmary and some private cases. The youngest child treated was 2 months, the oldest, 12 years old. Of the total cases treated 92 were colored and 32 white (table 1).

In the earlier part of the study the diagnosis of gonorrheal vulvovaginitis was based upon the finding of Gram negative intracellular and extracellular diplococci in vaginal smears. In the last year we have used cultural studies as well as Gram stained smears for diagnostic criteria. It is agreed that the results obtained by smear and culture are superior to those of smear or culture alone.

## METHODS

As soon as the diagnosis was established, the child, irrespective of age, weight, duration of symptoms, severity of disease or previous therapy, was given 1 mg of diethylstilbestrol<sup>2</sup> orally, three times a day,

## [Vulvovaginitis]

until 20 mg had been administered. The tablet was crushed and administered in 2 oz (60 cc) of cow's milk. The usual prophylactic methods and instructions were given to the mother, but the only form of therapy used was the diethylstilbestrol. The longest period of time in which treatment was continued was 3 weeks, but this was necessary in only two cases. The great majority were treated for only 1 week.

**Criteria of Cure** The criteria of cure were as follows. During the first year of study, smears were

TABLE 1. CASES

| Total cases | 124      |
|-------------|----------|
| White       | 32       |
| Colored     | 92       |
| Youngest    | 2 months |
| Oldest      | 12 years |

made weekly, until five consecutive negative smears had been obtained. At this point the child was considered cured. Smears were then made monthly and the child observed regularly in order to establish permanence of cure. In the last year of this study the smears have been supplemented by the use of cultures. Some of the children treated earlier were also checked by preparation of cultures. The cultures were made by Drs. Weiss and Colvin (2), Touro Infirmary, according to methods described by them. Any cases having consecutively negative smears and cultures for a period of at least 3 months were considered cured. Since we desired to check these children as frequently as possible for our own critical analysis we followed many for more than one year. Smears were studied for the presence or absence of the Neisserian diplococcus, pus cells and character of the epithelial cells present. The pH values were recorded in 50 patients by using nitrazine paper. The pH values reveal the fact that diethylstilbestrol is an agent

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With kindness of Mr. Kenneth Smoot.

whereby the normal alkaline pH of a child's vagina is quickly changed to a strongly acid reaction. The pH continues to be acid for about 4 weeks following discontinuance of therapy, and then it slowly becomes alkaline again (fig. 1). Vaginal biopsies and the presence of cornified epithelial cells with pyknotic nuclei

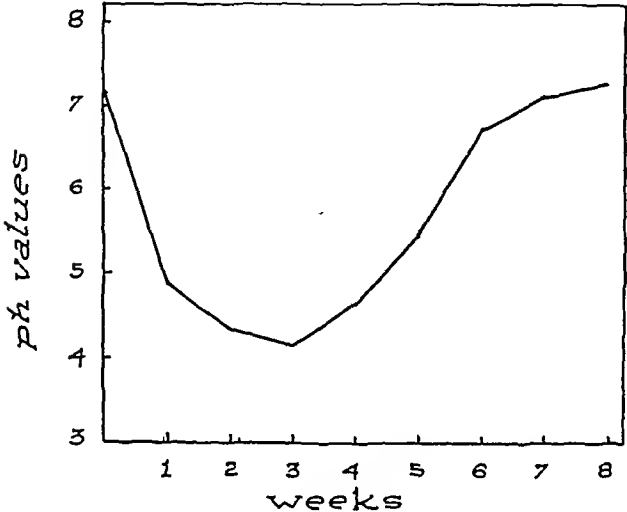


Fig. 1. COMPOSITE CURVE OF pH DETERMINATIONS OF 50 CASES OF INFANT VAGINITIS TREATED WITH DIETHYLSTILBESTROL

show that a transformation to an adult type of mucosa has taken place at the same time.

DISCUSSION OF RESULTS

In our earlier report we proved, by means of vaginal biopsy, that full estrogenic response was obtained in the vaginal mucous membrane, usually within a period of 7 days, by the administration of 1 mg. of diethylstilbestrol orally, three times daily. Coincident with the full estrogenic response, vaginal

TABLE 2. COMPLICATIONS

|   |     |
|---|-----|
| Pain about umbilicus                          | 25  |
| Nausea  | 6   |
| Vomiting                                      | 8   |
| Diarrhea                                      | 3   |
| Swollen pigmented nipples                     | 124 |
| Edema of labia majora                         | 22  |
| Tender nipples                                | 2   |
| No complications other than pigmented nipples | 84  |

mears showed the absence of pus cells and Gram-negative diplococci, only large epithelial cells containing much glycogen and small pyknotic nuclei being found.

These findings are in accord with the results obtained by administering estrogenic sterols in the form of vaginal suppositories, with the exception that usually 21 to 28 days are required to attain the same results when suppositories containing estrogenic terols are used. Recently Woodruff and TeLinde (3) in a study of 50 cases of infant vulvovaginitis treated with diethylstilbestrol concluded that gonococcal vaginitis can be successfully treated with the synthet-

ic estrogen, diethylstilbestrol. They found that 'the disease could be cured by oral administration as well as by suppositories, but our results were more uniformly successful and were obtained on an average more rapidly with the latter.'

We have not had any experience using suppositories of diethylstilbestrol in the treatment of infant vulvovaginitis. We are still using the same dosage of diethylstilbestrol, given over the same period of time and administered in the same manner as formerly, but it is planned to treat a series of cases using suppositories of diethylstilbestrol to compare the results with the present series. Experience with the larger series than was first reported gave no reason to vary the original plan. No patient was observed in whom toxic or unpleasant symptoms arising from the drug warranted its discontinuance. True, certain side ef-

TABLE 3. SMEAR AND CULTURE STUDY

| Period Followed | Repeated Negative Smears Unconfirmed by Culture | Repeated Negative Smears Confirmed by Culture | Recurrent Reinfections | Failures | Inadequately Followed | Total Cases Followed |
|-----------------|---|---|------------------------|----------|-----------------------|----------------------|
| 3 months        | 3   | 7   | 4                      | 0        | 6                     | 20                   |
| 3-6 months      | 10  | 7   | 3                      | 0        | 8                     | 28                   |
| 6 months-1 year | 2   | 2   | 1                      | 1        | 4                     | 10                   |
| 1-2 years       | 37  | 15  | 1                      | 1        | 0                     | 54                   |
| 2 years         | 11  | 1   | 0                      | 0        | 0                     | 12                   |
| Total           | 63  | 32  | 9                      | 2        | 18                    | 124                  |

fects were observed (table 2), but none was more than mild in nature and all regressed completely within two weeks following completion of therapy. The estrogenic response, as determined by the vaginal smear, usually persisted for a slightly prolonged period of time. No permanent change was observed in any patient, nor was any symptom observed that would make us hesitate to apply this form of therapy in any case of infant vaginitis.

Any case in which the patient failed to report for 5 consecutive weeks was considered to be inadequately followed even though all of the patients so classified had negative smears when last seen. There were a total of 106 cases with complete follow-up studies (table 3). Of this number 95 cures were obtained (90%), table 4. There were 9 cases of recurrences or reinfections and 2 failures. Of the recurrences or reinfections, all but 2 were cured by a

TABLE 4. PERCENTAGE OF CURES

| Period of Treatment | Number of Cases | Cases Cured | Percentage Cured | Reinfection, Recurrence | Percentage of Recurrence | Failure | Percentage Failures |
|---------------------|-----------------|-------------|------------------|-------------------------|--------------------------|---------|---------------------|
| 1 week              | 89              | 82          | 92               | 7                       | 7                        | 0       |                     |
| 10 days             | 0               | 8           | 80               | 1                       | 11                       |         |                     |
| 2 weeks             | 6               | 5           | 83               | 1                       | 16                       | 0       |                     |
| 3 weeks             | 2               | 0           |                  | 0                       |                          | 2       | 100                 |
| Totals              | 106             | 95          | 90               | 9                       | 8                        | 2       | 2                   |

second course of therapy. These two failures resisted attempts to obtain a cure by means of diethylstilbestrol or other types of therapy (table 5).

TABLE 5 RETREATMENT OF RECURRENCES, REINFECTIONS AND FAILURES

| Cases Followed                          | Negative Smear, No Culture | Negative Smear, With Culture | Failure |
|---|----------------------------|------------------------------|---------|
| Less than 3 months                      | 0                          | 0                            | 0       |
| More than 3 and less than 6 months      | 1                          | 3                            | 0       |
| More than 6 months and less than 1 year | 2                          | 3                            | 1       |
| More than 1 year                        | 0                          | 0                            | 1       |

| Treatment Period | Cases | Cures | Recurrence | Failure |
|------------------|-------|-------|------------|---------|
| 1 week           | 4     | 4     | 0          | 0       |
| 10 days          | 5     | 5     | 0          | 0       |
| 4 weeks          | 2     | 0     | 0          | 2       |

At the onset, the acute case of vulvovaginitis presented a thick, greenish yellowish discharge, which changed, within 36 to 48 hours after administration of diethylstilbestrol, to a thin mucous discharge. Smears and cultures made daily showed that the earliest negative smears and cultures were seen on the third day, and that a majority of cases presented negative smears and cultures 2 to 5 days following the administration of diethylstilbestrol.

#### CONCLUSION

1 After two years of experience in the use of diethylstilbestrol orally for the treatment of infant vulvovaginitis, we are as enthusiastic about its use as we were at the time of presenting our preliminary report.

2 We feel that diethylstilbestrol has definite advantages over other methods of treatment. They are: a) It can be administered orally. b) Cure is rapid and efficient. The length of time required for cure is far shorter than for any other method of therapy. c) The child is not rendered 'genital conscious,' and, in fact, is not aware that she is taking medicine. d) The expense is small. e) Its use provides an easy method for the control of possible widespread infection in institutions. f) The toxic effect is never enough to warrant discontinuance of the drug.

3 In the 106 cases considered adequately followed the rate of cure was 90%.

4 If the 18 cases are included who were negative at the time last seen, but who did not report for 5 consecutive weeks, the rate of cure is 122 of 124 cases, or 98 per cent.

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# Clinical Evaluation of Adjunctive Therapy with Stilbestrol Monomethyl Ether with Comments on Toxicity

## [[Stilbestrol Monomethyl Ether]]

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THAT ALL biological processes are essentially chemical in nature is becoming increasingly evident, especially in the field of reproductive physiology. Among the more significant of these advances has been the demonstration that estrogenic activity is the property of scores of compounds, many of which do not possess a steroid nucleus. The latter group includes the very potent synthetic estrogen, diethyl-dihydroxystilbene, which is also known as diethylstilbestrol.

The ultimate desideratum of estrogenic therapy is a compound that is efficacious orally, inexpensive and practically free from side reactions. To date, diethylstilbestrol has proven to be the compound most suitably meeting these requirements. In a small percentage of patients certain undesirable side-effects may occur usually of a gastrointestinal nature. In an effort to reduce these side-effects to a minimum the compound stilbestrol monomethyl ether has been prepared and submitted for clinical trial.

Since it has been shown that estrone methyl ether is probably demethylated into free estrone before being metabolized, it seemed plausible that demethylation of stilbestrol monomethyl ether was a prerequisite for its estrogenic action (1, 2). By administration of the monomethyl ether of stilbestrol, it was hoped that only small concentrations of the more active stilbestrol would thus become available in the body at any one time.

In the rat Geschickter found that, orally, diethylstilbestrol was from 2.5 to 5 times as potent as stilbestrol monomethyl ether. By injection, diethylstilbestrol was about 6 times as active. When 10 to 25 times the threshold dose was injected, however, the effect of the monomethyl ether was maintained approximately 3 to 10 times as long (3).

### CLINICAL EVALUATION

From December, 1940, to January, 1942, we have treated 120 patients. Approximately 96 per cent of these were colored.

#### *Severe Climateric Vasomotor Instability*

There were 97 cases in this group, of which 62 were surgical and 35 were spontaneous. The selection of patients was made in a manner previously described (4). Briefly, at the first visit the patient was carefully evaluated mentally as well as physically. If a history of nausea was elicited, an attempt was made to determine whether the nausea was caused by sensitivity to fried or fatty foods, or whether it was precipitated by the hot flashes, for it was found that many patients were nauseated with especially severe flashes. In addition, it was found that a small percentage of patients gagged on any type of pill, including lactose placebos.

For a period of 2 to 6 weeks each patient received sedation in the form of bromides or barbiturates. If the individuals were overweight, they were sent to a dietitian for advice. When indicated, the basal metabolic rate was determined. The patients were advised to avoid situations in which a strain would be placed upon the vasomotor system especially in regard to the heat regulating mechanism (5). In addition, each patient kept a daily written record noting separately the number of flashes experienced by day and after retiring at night. Placebos of lactose made up to look exactly like the tablets of stilbestrol monomethyl ether were frequently given both before and during therapy. When the drug was administered parenterally, injections of sterile oil or sterile water were often given both before and during the course of treatment. In this manner, it was possible to eliminate over 60 per cent of the patients who were sent to the Gynecological Endocrine Clinic with the diagnosis of 'menopausal syndrome.' Moreover,

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TABLE 1 DOSAGE OF STILBESTROL MONOMETHYL ETHER REQUIRED TO BRING MENOPAUSAL PATIENT INTO VASOMOTOR EQUILIBRIUM<sup>1</sup>

| Dose, <sup>2</sup><br>mg | Interval | Route     | Response <sup>3</sup> |    |        |    |          |    |      |    |           |    | Total<br>Number of<br>Patients |
|--------------------------|----------|-----------|-----------------------|----|--------|----|----------|----|------|----|-----------|----|--------------------------------|
|                          |          |           | None                  |    | Slight |    | Moderate |    | Good |    | Excellent |    |                                |
|                          |          |           | No                    | %  | No     | %  | No       | %  | No   | %  | No        | %  |                                |
| 0.1                      | Daily    | Oral      | 11                    | 55 | 5      | 25 | 2        | 10 | 2    | 10 | 0         | 0  | 20                             |
| 0.5                      | Daily    | Oral      | 7                     | 17 | 12     | 29 | 15       | 36 | 4    | 9  | 4         | 9  | 42                             |
| 1.0                      | Daily    | Oral      | 2                     | 4  | 11     | 20 | 14       | 25 | 17   | 30 | 12        | 21 | 56                             |
| 2.5                      | Daily    | Oral      | 0                     | 0  | 3      | 6  | 9        | 17 | 22   | 42 | 18        | 35 | 52                             |
| 5.0                      | Daily    | Oral      | 0                     | 0  | 0      | 0  | 1        | 7  | 7    | 50 | 6         | 43 | 14                             |
| 10.0                     | Weekly   | Injection | 1                     | 4  | 4      | 15 | 10       | 37 | 9    | 33 | 3         | 11 | 27                             |
| 25.0                     | Weekly   | Injection | 0                     | 0  | 2      | 8  | 2        | 8  | 15   | 57 | 7         | 27 | 26                             |

<sup>1</sup> Determined by the control of hot flushes<sup>2</sup> These do not represent maintenance doses<sup>3</sup> Response was graded as follows: None, no response; Slight, slight decrease in intensity of flushes; Moderate, definite reduction in number and intensity of flushes; Good, less than 5 mild flushes by day and occasionally one at night; Excellent, no flushes at night, occasionally one during the day

any patient who did not have flushes or sweats at night was also excluded, for it was found in the majority of these cases that psychogenic factors were the principal precipitating cause. In short, only those cases which could be classed as 'severe' menopausal syndrome were treated. The occurrence of hot flushes was the criterion used in judging the response of the patient. All other symptoms were considered secondary.

If, in spite of adequate sedation and mental reassurance, flushes and sweats were not controlled, stilbestrol monomethyl ether<sup>2</sup> was administered. The patient was instructed to take the tablets after the morning or evening meal. When the history was suggestive of a gallbladder syndrome or chronic constipation, a teaspoonful or two of magnesium sulfate also was prescribed each night.

In table 1 are summarized the results obtained on the various dosage levels. It should be noted that these do not represent the maintenance dose necessary to keep the patient in a state of well being, but rather the dosage required to bring the patient into vasomotor equilibrium. At first the smallest available dose (0.1 mg) was given for a period of 2 to 4 weeks, later as our experience increased, the starting dosage was increased. At present, 1 to 2.5 mg daily is used as the initial dosage. The dosage was maintained or increased until the flushes or sweats were practically abolished at night, while, if they occurred during the day, they were both mild and infrequent. At this point a state of vasomotor equilibrium was considered as established. After a period of 3 to 4 weeks on the dosage necessary to establish equilibrium, the amount

was gradually reduced, if possible, until a maintenance dose-level was secured. Peculiarly enough, it was found that the maintenance dose-level fluctuated in many patients. This was particularly evident when the weather was changeable, especially in the spring and fall. In addition, a psychic upset such as disagreement with a member of the family not infrequently disturbed the patient's vasomotor equilibrium. An attempt was made to keep the patient practically symptom-free for 3 to 6 months, or more, before discontinuing therapy.

In table 2 are analyzed the gastro intestinal side-effects that were observed during therapy. From the correlation of reactions and dosage levels it is evident that the higher the dosage the higher the percentage of side-reactions (4, 6). Furthermore, patients with a previous history of sensitivity to fried and fatty foods were noted to be much more prone to experience nausea at any given dosage level. Similar observations have been reported with the use of diethylstilbestrol.

Bleeding occurred in 5 of the 35 cases of natural menopause. In two, it was scanty and irregular; menopause had occurred one and two years earlier, respectively. As a rule, bleeding appeared while the dosage was being lowered, but therapy was not discontinued. In the third case, bleeding occurred after therapy was stopped. In the remaining two cases, the bleeding proved to be troublesome. Both of these were still having periods at more or less regular intervals. One of these received 25 mg by injection on the first day of an apparently normal menses. The flow increased markedly and 12 days later a curettage was performed. A well developed secretory endometrium was found. In the other patient, receiving 2.5 mg daily, menses became more regular but much more profuse and lasted 8 to 10 days. Endometrial biopsy on one of these occasions disclosed a secretory endometrium. In both of these patients therapy was discontinued although the pelvic findings were essen-

<sup>2</sup> Diethylstilbestrol monomethyl ether (Monomestrol) was supplied by Drs W. Salmon and F. C. Schmeltzer of Wallace and Tiernan Products Company, Belleville, N. J. Diethylstilbestrol (Estroben) was supplied by Mr. A. A. Ebby of Ayerst, McKenna & Harrison, Ltd., Rouses Point, N. Y. Estradiol dipropionate (Di-Ovocin) was supplied by Dr. E. Oppenheimer of Ciba Pharmaceutical Products, Inc., Summit, N. J.

tially normal. When methyl testosterone was given orally to these 2 patients the flushes were relieved. Bleeding, when it occurred, was normal in amount.

In summary, then, bleeding proved troublesome in two, or approximately 6 per cent of the treated cases of spontaneous menopause. It should be emphasized that bleeding may become an annoying symptom, but usually only in those patients who are still menstruating more or less regularly.

TABLE 2. COMPARISON OF GASTRO-INTESTINAL SIDE-REACTIONS EXPERIENCED BY PATIENTS WITH PREVIOUSLY NEGATIVE GASTRO-INTESTINAL HISTORY (Group V) AND THOSE NOTED IN PATIENTS WITH A POSITIVE HISTORY OF SENSITIVITY TO FRIED AND FATTY FOODS (Group IV)

| Dose, Route, mg.   | Total on Dose | Previous G.I. History | No. of Each | Nausea |    | Total with Nausea, % |
|--------------------|---------------|-----------------------|-------------|--------|----|----------------------|
|                    |               |                       |             | No.    | %  |                      |
| 0.1, oral; daily   | 20            | Negative              | 15          | 0      | 0  | 0                    |
|                    |               | Positive              | 5           | 0      | 0  |                      |
| 0.5, oral; daily   | 42            | Negative              | 28          | 0      | 0  | 0                    |
|                    |               | Positive              | 14          | 0      | 0  |                      |
| 1.0, oral; daily   | 56            | Negative              | 42          | 0      | 0  | 2                    |
|                    |               | Positive              | 14          | 1      | 7  |                      |
| 2.5, oral; daily   | 52            | Negative              | 41          | 0      | 0  | 2                    |
|                    |               | Positive              | 11          | 1      | 9  |                      |
| 5.0, oral; daily   | 14            | Negative              | 10          | 3      | 30 | 36                   |
|                    |               | Positive              | 5           | 2      | 40 |                      |
| 10.0 hypo.; weekly | 27            | Negative              | 18          | 1      | 6  | 7                    |
|                    |               | Positive              | 9           | 1      | 11 |                      |
| 25.0 hypo.; weekly | 26            | Negative              | 16          | 1      | 6  | 11                   |
|                    |               | Positive              | 10          | 2      | 20 |                      |

In 23 instances, it was possible to compare the effectiveness of stilbestrol monomethyl ether with diethylstilbestrol<sup>2</sup> orally. In 18 cases, mg. for mg., diethylstilbestrol proved to be approximately 5 times as effective as stilbestrol monomethyl ether.<sup>3</sup> The average for the group disclosed that diethylstilbestrol was 5.4 times as effective, comparing fairly well with experimental data (3).

<sup>3</sup> This was determined in the following manner. Patients were secured who were in fairly good vasomotor equilibrium, having from 2 to 5 flushes daily and rarely one at night. After 4 weeks on the same dose level of stilbestrol monomethyl ether with no improvement, the therapy was changed to diethyl stilbestrol, using one-tenth the dose of the monomethyl ether. If necessary, the dose of diethyl stilbestrol was raised at two-week intervals until a more stable vasomotor equilibrium was reached and maintained. In a similar manner it was found in 4 patients that, dose for dose, estradiol dipropionate was 15 to 20 times as efficacious as stilbestrol monomethyl ether when administered intramuscularly in sesame oil.

Essential Senile Vaginitis

There were 7 patients in this group including one with mild generalized essential senile pruritis. In each case, after excluding all other constitutional and local causes, relief was secured mainly by local therapy. Once a week a tampon of non-absorbent cotton coated with 25 mg. of stilbestrol monomethyl ether in sesame oil was inserted and left in place for 48 hours. A douche twice a day with a quart of lukewarm water containing 8 tablespoons of household vinegar was prescribed following removal of the tampon.

The patient with the essential senile pruritis was 72 years old. The vaginitis was of about two years' duration and in the last 6 months it had become much more severe. During this time she observed that she had a generalized itch all over her body. Many scratch marks bore evidence to this. The vaginitis cleared up with local therapy. Dermatological consultation confirmed the diagnosis of essential senile pruritis. She was placed on a high vitamin, high caloric diet with no relief. On oral therapy with stilbestrol monomethyl ether, some relief was obtained with 1 mg. daily. The prescription was changed to oral diethylstilbestrol, 1 mg. daily, with complete alleviation of the itching. In the relief of essential senile pruritis, we had previously found that estradiol and testosterone were practically specific (7). This is the second case observed in which complete relief of the essential senile pruritis was obtained with diethylstilbestrol. We have found that pellets are the ideal method of administration since this condition requires continuous therapy (4).

Galactorrhea

There were 4 cases in this group. Two were cases in which abortion had occurred 8 and 10 months before, respectively. Two were of that rare group of cases of post-hysterectomy lactation. No evidence of pregnancy was noted in the surgical specimens. In one, a supravaginal hysterectomy and a left salpingo-oöphorectomy was done. The breasts filled and lactation occurred 10 days later. The other, from whom both ovaries and uterine fundus had been removed, began to lactate a week following the operation.

In each of these 4 cases, regardless of the dosage of stilbestrol monomethyl ether (up to 50 mg. weekly), the amount of breast secretion either remained the same or actually increased. In short, the estrogen was ineffective in suppressing lactation. Methyl testosterone and testosterone propionate also had no effect. Negative results have been observed also with diethylstilbestrol (8) and estradiol (9).

Primary Dysmenorrhea

There were 6 patients in this group. In 4 dysmenorrhea had been of a mild character until an at-

tack of pelvic inflammatory disease had aggravated it. In only one of this group of 4 was any relief secured. She received 25 mg. of stilbestrol monomethyl ether a week by injection throughout the cycle. As soon as therapy was discontinued, the periodic pains returned. Of the two uncomplicated cases, only one was fully relieved by 5 mg. daily. In this case, too, relief occurred only while on therapy. In short, the results were not entirely satisfactory.

#### Secondary Amenorrhea

There were 6 cases in this group. In only 2 was any degree of success achieved. The first of these patients, aged 20 years, had had very irregular menses for the past year. For the last 4 months she had been amenorrheic. On examination, an infantile uterus was found. She also complained of sterility since her marriage 9 months before. With thyroid up to 3 grains daily for 2 months, no menses appeared. She was then given 50 mg. of stilbestrol monomethyl ether weekly for 3 doses. Eleven days later she menstruated. This therapy was repeated with similar results. The third time she remained amenorrheic for 10 weeks. On examination she was found to be pregnant. Seven months later she delivered a normal female infant. The second successful result was in a patient given combined thyroid and estrogenic therapy for 4 months. The other 4 cases failed to respond. It should be noted that 3 of these cases had previously failed to respond to therapy with pregnant mare serum.

#### COMMENT

The results obtained with stilbestrol monomethyl ether in the management of the menopausal patients demonstrate that it is therapeutically effective orally. Since gastro intestinal side reactions occurred almost exclusively in the menopausal patients, it would be profitable to analyze them in detail. Careful study reveals that gastrointestinal side reactions to diethyl stilbestrol or other of the stilbestrol derivatives may be divided into 5 groups.

Group I consists of those individuals who are unable to take any sort of pill by mouth. They gag and are nauseated even on lactose placebos. In these patients no nausea was noted on injection therapy. Such instances as these are considered incidental side reactions.

Group II includes those patients who become nauseated only while receiving simultaneously some other medication such as digitalis, intravenous neoarsphenamine or ferric ammonium citrate. In other words, the nausea or vomiting cannot be blamed exclusively upon the estrogen, for any one of these other drugs alone may cause nausea. These instances also are not considered true side reactions but as merely incidental ones.

Group III includes those patients who become nauseated or 'sick to the stomach' concomitantly with their flushes. This is particularly evident on arising in the morning, a type of 'morning sickness' in the menopausal woman. In each instance, simultaneous with relief from the hot flushes by suitable therapy, the nausea disappeared. Not infrequently the flushes may actually be accentuated at the beginning of therapy (5), thus aggravating the nausea. This type of response also does not fall in the category of true side reactions.

TABLE 3 GASTRO INTESTINAL SIDE REACTIONS IN PATIENTS WITH PREVIOUS HISTORY SUGGESTIVE OF Gall Bladder Syndrome COMPARED WITH THOSE OF NORMAL PATIENTS

|  | No of Cases | No with Nausea | Ratio | Per Cent | $\bar{x}/\sigma^1$ | Probability of Error |
|--|-------------|----------------|-------|----------|--------------------|----------------------|
| Previous history of gall bladder syndrome* | 15          | 5              | 1/3   | 33       | 3.185              | 0.024                |
| Negative G.I. history                      | 82          | 5              | 1/16  | 6        |                    |                      |
| Total                                      | 97          | 10             | 1/10  | 10       |                    |                      |

\*It should be noted that the factor of dose level has been excluded here on the basis that the 'scatter' was fairly even especially on the higher dose levels.

<sup>1</sup> Pearl R. Medical Biometry and Statistics. Chap. X and XI, Second edition. 1930. Saunders Philadelphia.

Group IV consists of those patients whose past history reveals marked sensitivity to fried or fatty foods, accompanied by nausea, vomiting, severe heartburn and eructation. Clinically these symptoms are suggestive of a 'gall bladder' syndrome. Fifteen patients gave such a history. Of these, 5 became nauseated on stilbestrol monomethyl ether. One patient, receiving 1 mg. daily, orally, experienced no further nausea following cholecystectomy. A second patient, who was taking 5 mg. daily orally, was relieved by reducing the dose, while taking 1 mg. of diethylstilbestrol daily she experienced no nausea and at the same time was completely relieved of the flushes. The remaining 3 patients were relieved of the nausea by taking either two teaspoonfuls of magnesium sulphate or 100 mg. of desoxycholic acid nightly. One of these patients was nauseated by 5 mg. daily by mouth and 25 mg. weekly by injection. A second one was nauseated by both 25 mg. and 10 mg. weekly.

Group V is made up of those patients with a negative gastrointestinal history who develop nausea only while receiving estrogenic therapy. In this series, there were 5 cases. In 2, the nausea was inconstant and disappeared in time. Two others were relieved

by reducing the dosage and gradually increasing it again. The fifth was relieved by changing from hypodermic to oral therapy.

When we exclude the patients in Groups I, II and III, we note that there were 10 patients with true gastro-intestinal side-reactions. Of these, 5 were of the group who gave a previous history suggesting a 'gall bladder syndrome.' The data are summarized in table 2. It is noted that patients giving a previous history suggestive of a gall bladder syndrome are much more prone to experience nausea, than those with a negative gastro-intestinal history. Statistical analysis (table 3) reveals that these figures are sig-

TABLE 4. INCIDENCE OF NAUSEA ENCOUNTERED AT VARIOUS DAILY ORAL DOSE LEVELS OF DIETHYLSTILBESTROL AND STILBESTROL MONOMETHYL ETHER<sup>1</sup>

| Dose, mg. | Incidence of Nausea, % |                              |
|-----------|------------------------|------------------------------|
|           | Diethyl stilbestrol    | Stilbestrol monomethyl ether |
| 0.1       | 1.3                    | 0                            |
| 0.25      | 3.4                    |                              |
| 0.5       | 5.3                    | 0                            |
| 1.0       | 12.1                   | 1.8                          |
| 2.5       |                        | 1.9                          |
| 5.0       | 41.7                   | 35.8                         |

<sup>1</sup> In making the comparison it should be noted that, orally, diethylstilbestrol is at least 5 times as potent as stilbestrol monomethyl ether.

nificant, even for various dose levels. Similar observations in patients receiving diethylstilbestrol have been reported (4). The explanation for the greater tendency of patients in Group IV ('gall bladder' syndrome) to experience nausea remains to be found. In the guinea pig it has been shown that estrogen will cause a delay in the emptying time of the gall bladder (10, 11). Such an effect, if proven in the human female, would account for the increased sensitivity to estrogens in patients of the type in Group IV. It would also explain the correlation between the higher dosage, and the greater incidence of side-reactions.

Another factor of considerable importance in evaluating the side-reactions under discussion is the relative estrogenic potency of the substance in question. For example, in this diethylstilbestrol was found to be about 5 times as potent, mg. for mg., as stilbestrol monomethyl ether. When the incidence of side-reactions to both substances is compared on a potency basis, it is found to be essentially the same (table 4). Similar observations have been noted by others (6, 12).

*Galactorrhea.* The physiologic pathology of this condition is still not clear. On the basis of our present knowledge, the reason for the failure of diethylstilbestrol or the monomethyl ether of stilbestrol to affect the secretion may be hypothesized. Diethylstilbestrol may stimulate the increased production of lactogenic hormone by as much as 226 per cent (13). Thus, indirectly diethylstilbestrol actually stimulates lactation. In fact, lactation has been initiated in virgin goats (14), and partially, in the human female (15), by the use of diethylstilbestrol plus active massage or pumping of the mammary gland.

*Essential senile pruritis.* Just recently this syndrome was declared to be one of the unsolved problems of medicine (16). Preliminary experience with estradiol and testosterone demonstrated that these steroids were extremely effective in relieving pruritis. Our preliminary findings with diethyl stilbestrol and the monomethyl ether of stilbestrol, if confirmed, should prove a boon to patients with essential senile pruritis.

*Oral mucous membranes.* Pre-treatment biopsies of the buccal mucous membrane revealed varying degrees of atrophy in some patients. After adequate treatment the buccal mucosa showed the same histological picture of estrogenic stimulation as did the vaginal mucosa. These studies will be reported in detail elsewhere (17).

In its broader aspects, these are two more examples of the fact that the so-called sex hormone substances are fundamentally constitutional drugs, irrespective of their effects on the secondary sexual apparatus.

#### SUMMARY AND CONCLUSIONS

Adjunctive therapy with stilbestrol monomethyl ether, as with other estrogens, has shown that it is a), of definite value in the management of climacteric vasomotor instability and senile vaginitis including essential senile pruritis; b) it is of very limited value in the management of secondary amenorrhoea and dysmenorrhoea; and c), it is of no value in management of galactorrhea.

Analysis of gastro-intestinal side-reactions to therapy with stilbestrol monomethyl ether reveals that the greater the dosage, the greater the incidence of side-reactions. Patients with a previous history of sensitivity to fried and fatty foods are more prone to suffer nausea than are patients with a negative gastro-intestinal history. When stilbestrol monomethyl ether is compared with diethylstilbestrol on a potency basis, the incidence of nausea is similar if given orally.

In 35 cases of spontaneous menopause receiving treatment with stilbestrol monomethyl ether bleeding proved to be troublesome in two or 6 per cent.

An atrophic buccal mucosa was proved by biopsy to be restored to normal after treatment.

Orally, diethylstilbestrol was found to be at least 5 times as potent as the monomethyl ether of stilbestrol

When injected in sesame oil, estradiol dipropionate was found to be from 15 to 20 times as potent as stilbestrol monomethyl ether, mg for mg

The author is indebted to Drs P. E. Crooks and E. Matlin for their kind assistance in carrying out these studies

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# Effect of Inunction of Alpha Estradiol and of Oral Medication with Pregneninolone upon Postmenopausal Human Uterus

## [[Postmenopausal Endometrium]]

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NEUSTAEDTER (1), using 120 mg. of synthetic  $\alpha$ -estradiol and 900 to 1200 mg. of pregnenolone, both given by mouth, was able to produce proliferation and subsequent secretory changes in the endometrium of 6 women, ranging in age from 22 to 40 years, who had been surgically castrated.

The present study was made to determine whether similar changes could be produced in women in the menopause after bleeding had ceased spontaneously for a considerable length of time, in these instances, from 1 to 7.5 years, and in whom marked atrophy of the uterus, cervix and vagina was present.

Six patients were studied. All had atrophic or resting endometrium prior to treatment. In 3 cases there was such a marked atrophy of the endometrium that it was impossible to obtain endometrial tissue for premedication biopsies, even after vigorous curettage. The patients were given an ointment containing 1 mg. of synthetic  $\alpha$ -estradiol per gm. of ointment, and were instructed to use it by inunction, from 1 to 2 gm. daily for 1 month. After 2 weeks they were given 100 to 120 mg. of pregnenolone orally per day for 10 days. In two of the cases the course of therapy was repeated.

Subsequent endometrial biopsies revealed the following: a). After 2 weeks of estradiol therapy by inunction, endometrial biopsy specimens from each of the 6 cases revealed proliferation of the endometrium. b). After combined estradiol inunction and oral pregnenolone therapy, the endometrium in 4 of the 6 cases showed secretory changes.

The 6 patients had suffered from menopausal symptoms, mild to severe in degree, consisting of flushes, sweats, headaches, and nervousness, for some time. These complaints were completely relieved during the course of therapy. However, after cessation of treatment, these symptoms recurred, usually within 5 to 10 weeks.

### CASE REPORTS

Case 1, R.F., aged 49, white female, married, having 3 adult children. Onset of menses was at 14 years, with 3-day periods of moderate flow, associated with dysmenorrhea, occurring regularly every 28 days. Menopause with rather severe symptoms, consisting of flushes, sweats, vertigo, and headaches, began 18 months previously. Last bleeding episode was in July, 1940. The last previous bleeding took place in November, 1939. Basal metabolic rate was -14 per cent. Hormone study revealed a negative prolan reaction and 8.5 R.U. of estrin per 24-hour specimen. A biopsy performed on May 6, 1941 demonstrated almost complete atrophy of the endometrium, and no tissue was obtained. On May 13, biopsy produced an endometrial mucosa with an occasional gland. A diagnosis was made of a very early proliferative phase. Estradiol ointment, 2 gm. daily, was given between May 13 and June 3. On June 3 the biopsy report indicated an early proliferative phase, more advanced than in the previous biopsy. Estradiol ointment, 2 gm. per day, combined with 100 mg. of pregnenolone orally was given daily for 10 days, from June 3 to 12, at which time the patient began to bleed, and stained for 6 days. The biopsy made at the beginning of bleeding revealed a late proliferative and early secretory phase. The patient felt very well at this time, and had no complaints. Her condition continued satisfactory for 6 weeks, by which time she was again suffering from some menopausal symptoms.

Case 2, L.M., aged 53, white female, married, para ii. Onset of menses was at 14 years, with 4-day periods of moderate flow, without pain, occurring regularly every 28 days. The last menstrual period was 7 years ago, at which time menopausal symptoms began. The basal metabolic rate was +4 per cent. Hormone determinations revealed a positive prolan and a negative estrin reaction. On examination, the uterus was found to be 2.5 inches long, anterior, firm and freely mobile. No adnexal pathology was present. An endometrial biopsy was made on May 8, 1941 and no tissue was obtained. Between May 8 and May 15, estradiol ointment, 1 gm. daily, was administered by inunction. On May 15, a biopsy specimen of the endometrium showed an early proliferative phase.

FIG 1, A AND B RESTING AND EARLY SECRETORY PHASE respectively, of endometrium of case 3, before and after therapy



FIG 2, A AND B RESTING AND LATE SECRETORY PHASE respectively, of endometrium of case 6 before and after therapy



From May 15 to June 5 estradiol ointment, 2 gm daily, was used, on June 5 a biopsy specimen of the endometrium revealed an early proliferative phase more advanced than in the previous specimen. Between June 5 and June 17, estradiol ointment, 2 gm daily, and 100 mg of pregnenolone daily, were given for 12 days. On June 17, an endometrial biopsy showed a proliferative reaction. The menopausal symptoms were entirely controlled at this time. Another course of therapy was given. From June 19 to July 10, estradiol ointment, 2 gm daily, and between July 11 and July 21 estradiol ointment, 2 gm and 120 mg of oral pregnenolone, were administered for 12 days. Biopsy of the endometrium still indicated a proliferative phase. The patient's menopausal flushes, sweats, headaches, and nervousness had disappeared, and 2 weeks thereafter she was still symptom free.

Case 3, D T, aged 43, white female, married, para 1. Onset of menses was at 12 years, with 4 day periods of moderate flow, without pain, occurring regularly every 28 days. The patient had her last menstrual period 1 year ago, and simultaneously climacteric symptoms consisting of sweats, flushes, vertigo, and headaches had set in. Hormone determinations showed a positive prolactin and negative estrin reaction. Pelvic examination revealed the

uterus to be 2.75 inches long, and retroverted. There was no adnexal pathology. On March 6, 1941 an endometrial biopsy was made but very scant shreds of tissue which were insufficient for diagnosis were obtained. From March 6 to March 27 estradiol ointment, 1 gm daily was administered by injection, and biopsy of the endometrium at this time demonstrated a proliferative reaction (fig 1, A). Between March 27 and April 10 estradiol ointment, 2 gm daily was given and from April 11 to April 22 estradiol ointment 2 gm and 100 mg of pregnenolone were administered daily for 11 days. On April 24, an endometrial biopsy was performed and an early secretory phase was found (fig 1, B). The patient stated that she felt fine, and was asymptomatic. The patient continued without complaints when last seen, on July 24, 1941.

Case 4, R F, aged 43, white female, married. Onset of menses was at 12 years, with 3 day periods of moderate flow without pain occurring regularly every 28 days. The patient had had 2 full term pregnancies. Severe menopausal symptoms consisting of frequent flushes, sweats, vertigo and occipital headaches started 1 year ago. The last bleeding episode occurred in July, 1940. Basal metabolic rate was -7 per cent. Hormone analyses showed that urinary prolactin was positive, estrin negative. A biopsy



made prior to treatment showed an early proliferative endometrium. Pelvic examination revealed the uterus to be 2.5 inches long, anterior and freely movable. No adnexal pathology was demonstrable. Estradiol ointment, 1 gm. daily, was given by inunction from Dec. 12, 1940 to Jan. 13, 1941. Then estradiol ointment, 1 gm. and 10 mg. of pregnenolone daily, was administered for 11 days. On Jan. 23, an endometrial biopsy demonstrated an early proliferative phase, but more advanced than in the original biopsy. The course of therapy was repeated, using larger doses of pregnenolone. From Jan. 23 to Feb. 6 estradiol ointment, 2 gm. daily, was used by inunction, and between Feb. 6 and Feb. 17, estradiol ointment 2 gm. plus 100 mg. of pregnenolone were administered. An endometrial biopsy made on Feb. 17 revealed a late proliferative and early secretory phase. A third course of therapy was instituted, similar to the second, treatment being continued from June 24 to July 17. On this latter date, and after the patient had been bleeding for 5 days, the endometrial biopsy showed a resting endometrium.

*Case 5, F.L.,* aged 44, married for 11 years, para i. Onset of menses was at 13 years, occurring regularly every 28 days, the flow was moderate in amount and painless. the patient had her last menstrual period 1 year ago, when climacteric symptoms of moderate degree set in consisting of sweats, flushes and headaches. Pelvic examination revealed the uterus to be 2.5 inches long and freely movable. There was no adnexal pathology. The basal metabolic rate was +9 per cent. Hormone determinations demonstrated a negative prolactin and a negative estrin reaction. An endometrial biopsy was made on May 6, 1941, and an early proliferative phase found. From May 6 to May 27 estradiol ointment, 1 gm. daily, was administered by inunction, and on May 27 a biopsy specimen revealed a late proliferative phase in the endometrium. Between May 27 and June 5 estradiol ointment, 1 gm. and 100 mg. of pregnenolone were given daily, for 10 days. A biopsy taken on June 5 indicated an early proliferative phase in the endometrium. On June 6 bleeding occurred and lasted 3 days. The course of therapy was repeated, except that 120 mg. of pregnenolone daily was administered along with the estradiol. On July 15, at the end of treatment, an endometrial biopsy showed areas of marked proliferation. The patient's menopausal symptoms were completely controlled by this time. On July 18, bleeding took place. Menopausal complaints recurred 5 weeks after cessation of therapy.

*Case 6, M.G.,* aged 51, married for 26 years, had 5 children and 4 miscarriages. Onset of menstruation was at 11 years, with 4-day periods of moderate flow, without pain, occurring regularly every 28 days. Last menstrual period was in October, 1940. Pelvic examination revealed the uterus to be 3 inches long, retroverted and freely movable. No adnexal pathology was present. Basal metabolic rate was -13 per cent. The hormone tests showed a positive prolactin and negative estrin reaction. The vaginal smears indicated a marked deficiency in estrogenic activity. An endometrial biopsy was made on May 6, 1941 and an early proliferative phase found. From May 6 to May 27 estradiol ointment, 1 gm. daily, was administered by inunction. On May 27, a biopsy of the endometrium re-

vealed a more advanced proliferative phase than in the tissue obtained on May 6 (fig. 2, A). Between May 27 and June 5 estradiol ointment, 2 gm., plus 100 mg. of pregnenolone, were given daily for 10 days. Endometrial biopsy performed on June 5 demonstrated an early secretory phase (fig. 2, B). During this time the patient suffered no menopausal symptoms. Vaginal bleeding occurred from June 7 to June 11, and was moderate in amount. On July 3 the patient complained that the menopausal symptoms were recurring, and on July 10 vaginal bleeding took place again. By this time the headaches, sweats, flushes and nervousness were quite severe.

#### COMMENT

Salmon, Walter, and Geist (2) produced progestational reactions in the endometrium of 5 postmenopausal women using doses of pregnenolone ranging from 105 to 540 mg. The endometrium in each case was first primed with from 120,000 to 655,000 R.U. of estradiol benzoate, injected intramuscularly.

Neustaedter produced progestational changes in the endometrium of 6 surgically castrated women with 1200 mg. of pregnenolone, given by mouth. The uteri were first primed with 120 mg. of synthetic estradiol, likewise administered orally.

In the present series of cases of 6 women, by giving adequate doses of pregnenolone, progestational changes in the endometrium were obtained in 4 cases after a preliminary period of priming by inunction with synthetic estradiol.

#### SUMMARY

1. Six postmenopausal women were treated with synthetic estradiol by inunction and pregnenolone orally. An average of 45 to 60 gm. of estradiol ointment, containing 45 to 60 mg. of the hormone, and 1000 to 1200 mg. of pregnenolone were used.
2. A proliferative reaction was produced in the endometrium in all 6 cases following estradiol inunction.
3. Following the combined administration of estradiol by inunction and pregnenolone orally, 4 of the 6 cases showed definite secretory changes in the endometrium.
4. All menopausal symptoms disappeared during the course of treatment.
5. Five to 10 weeks after cessation of treatment menopausal symptoms recurred.
6. All patients bled 1 to 3 days after cessation of treatment.

We wish to thank Dr. L. Pirk of Roche-Organon, Inc. for the supply of estradiol ointment, which was especially prepared for our purposes, and for the pregnenolone (Progestoral), the two preparations used in this study.

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# Simmonds' Disease: Report of Two Cases Caused by Intracranial Tumors

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BETWEEN 1914, when Simmonds first suggested that the clinical syndrome now named for him is the result of severe hypofunction of the anterior lobe of the pituitary, and 1940, when Escamilla and Lissner (1) reviewed the literature and their own practice, 595 cases have been diagnosed Simmonds' disease. Of these, only 101 were proved by necropsy. Although many of the other cases seemed typical clinically, analysis of the reported data led these authors to suspect that they were really examples of anorexia nervosa (1). The latter condition, they and others (2, 3), have considered most difficult to differentiate from hypopituitarism. Indeed, a chief purpose of their extensive review (1) was to establish criteria for differential diagnosis. In this connection, Case 1 is interesting, as at first the diagnosis of anorexia nervosa seemed well established.

Stephens (4) has recently pointed out that the sodium deprivation regimen described by Cutler, Power, and Wilder (5) as a test for Addison's disease can be useful in establishing the diagnosis of Simmonds' disease because of the secondary type of adrenocortical insufficiency present in these cases. Sheehan (6) and others (7) have reported that hypopituitarism may simulate myxedema and have warned that such cases may be dangerously susceptible to the action of thyroid. From this viewpoint, Case 2 is of interest, as the diagnosis of Addison's disease was made early in the course of his illness, was apparently confirmed by salt deprivation, and was evidently improved by desoxycorticosterone acetate. He, also, presented features suggestive of hypothyroidism and for a prolonged period had a favorable response to thyroid medication.

## CASE REPORTS

Case 1 J. D., an 18 year-old, white male, was admitted on July 26, 1940, complaining of loss of weight and polyuria during the past year.

Past history Enuresis had been present since infancy. At 5, he contracted scarlet fever, followed in succession by measles, pertussis, cervical adenitis, which required incision and drainage, and otitis media. Thereafter, he remained in good health until the onset of his present illness, although he never gained weight satisfactorily.

Social history The patient's mother died when he was 6. Until he was 12, he did fair work in school, being cared for during this time by his grandmother. Then his father remarried, and the patient exhibited deep resentment toward his stepmother. At the same time, his school work deteriorated, and he became a behavior problem. He associated with a bad gang, truanted, engaged in petty thievery, resorted to masturbation, lost interest in school, and was eventually expelled in the middle of the ninth grade. At the age of 16, he was referred to the Judge Baker Guidance Center, where he was noted to have an I. Q. of 99, to be 17 per cent underweight, to be slow in pubertal development, to have defective vision and headaches after reading, as well as frequent nocturnal enuresis. After leaving school the patient worked intermittently as a soda fountain clerk.

Present illness In the summer of 1939 the patient first noted that he was passing an unusually large volume of urine, that his enuresis was more constant, and that his fluid intake was excessive. However, he felt well until early fall, at which time he weighed 125 lb., his peak weight. Height was 5 feet, 8½ inches.

He then began to vomit after nearly every meal without any abdominal pain or obvious cause. Weight loss soon became alarming. He was admitted to two other hospitals for study, but no reason for the vomiting was discovered. At times he would improve, but, except for cessation of enuresis in January, 1940, his condition remained little changed until admission to the Massachusetts Memorial Hospital, at which time he weighed 93½ lb. (42.5 kg). Prior to admission, partial control of his polyuria had been achieved with pitressin by subcutaneous injection, but this caused abdominal cramps and further vomiting.

Physical examination The patient was fairly well developed, but extremely thin. He was cooperative, well oriented, and able to give a good account of the details of his illness and of the treatment he had received. Skin was rough, cool, and dry. Hair on the head was red, dry, and abundant. Hair on the body was very scanty. A few, fine,

light hairs were present on the forearms and legs; axillary hair was almost non-existent; and pubic hair was sparse, light, short, and confined to a small area. Pupils reacted normally. There was no apparent visual disturbance. Ophthalmoscopic examination showed discs that were questionably pale; fundi were otherwise not remarkable. Lungs, heart, and abdomen were not abnormal. Reflexes were present in the arms, but in the legs the reflexes were very sluggish and could not always be elicited, although there were no pathological reflexes. Blood pressure was 82 mm. Hg, systolic and 48, diastolic.

*Laboratory data.* When the patient was not taking posterior pituitary the urinary specific gravity ranged

peated on 11/20/40, the values were: fasting, 91; 1 hour, 138; 2 hours, 88; 3 hours, 102.

Total protein on 8/29/40 was 5.1 gm. per cent; albumin, 3.8 gm. per cent, and globulin, 2.35 gm. per cent. Blood cholesterol was 194 mg. per cent.

Basal metabolic rate was always low. Extreme ranges were from minus 37 to minus 17 per cent. Roentgen rays of the skull showed no evident pathology.

*Clinical course.* As can be seen in figure 1, the patient's urinary output was definitely in excess of his fluid intake during his first 18 days in the hospital. During this period he ate very little, vomited occasionally and lost weight slowly but steadily. He was very lethargic mentally and

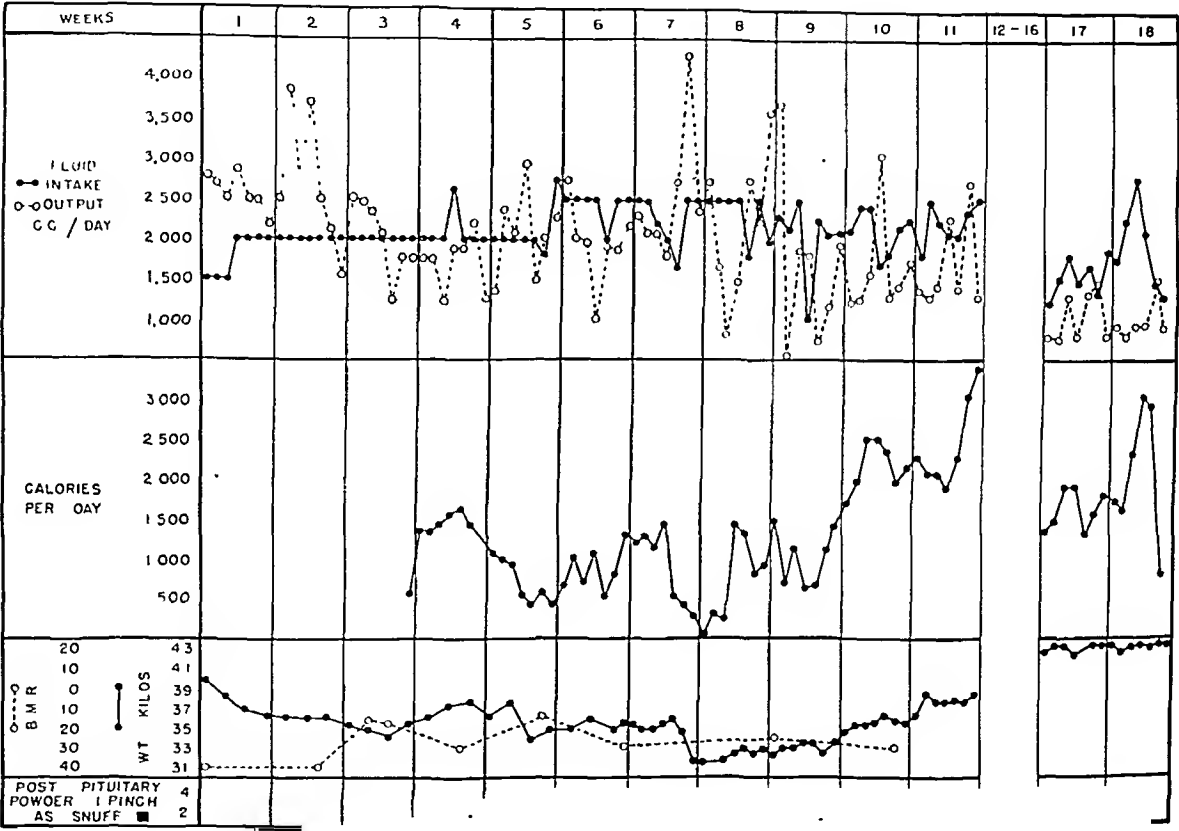


FIG. 1. Case 1. SUMMARY OF FLUID AND CALORIC BALANCE in relation to the use of posterior pituitary powder.

generally between 1.002 and 1.004. Otherwise, the urine was not remarkable.

Hinton reaction on the blood was negative. Hemoglobin was 85 per cent on admission with red blood cell count of .2 million, and white blood cell count of 11,800 with 72 per cent polymorphonuclears, 22 per cent lymphocytes, per cent monocytes, and 1 per cent eosinophils. During is stay, hemoglobin dropped to 70 to 75 per cent with ed cell count ranging around 3.5 million. White cell count emained normal, but there was a gradual development of lymphocytosis that persisted until discharge. During his ast 3 months in the hospital, he showed an eosinophilia of from 2 to 5 per cent.

Oral glucose tolerance test with 100 gm. of glucose on 7/29/40 gave values in mg. per 100 cc.: fasting, 90; 30 min., 150; 2 hours, 150; 3 hours, 183; 4 hours, 90. Re-

physically, seeming quite content to lie motionless in bed for long periods. Although he answered questions readily, his conversation was very superficial. It was impossible to interest him in anything. He had no expressed desire to regain his health. During this period, fasting blood sugar at the beginning and end of a 36-hour fast was 70 mg. per cent.

Patient was now given posterior pituitary powder by nasal insufflation. There was an immediate response. Urine output decreased. Vomiting stopped and appetite improved. Weight increased slightly, but steadily. Two weeks later, however, the powder appeared to lose its effectiveness. Subcutaneous injections of pitressin were tried for two days. This controlled urine output, but vomiting recurred, appetite failed sharply, and weight dropped. The patient complained of abdominal cramps,

and the descending colon and sigmoid could be felt as a tender, hard cord. Powder by nasal insufflation was resumed with increased dosage, and again he responded favorably.

Two weeks later the supply of posterior pituitary powder became exhausted, and all untoward symptoms recurred. At this time some whole gland pituitary powder was substituted without noticeable effect. Readministering posterior pituitary powder gave the same dramatic results as previously. He now began what proved to be a persistent improvement, which coincided with the institution of a regimen designed to stimulate his interest in his surroundings. He was obliged to have a hot tub bath every morning and to stay up most of the day. He was given light ward duties and was made to complete them.

During his first 3 weeks in the hospital, the patient was offered a high vitamin, high calorie diet with added brewer's yeast tablets (2.4 gm daily). He took very little of his diet and by the 18th day his tongue was a beefy red. Addition of nicotinic acid (0.24 gm daily) was soon followed by reversion of the tongue to normal. One month later, nicotinic acid was stopped for 5 days. Again, the tongue became red and raw looking, and again reverted to normal with resumption of the vitamin. About the same time, fissures became evident at the corners of the mouth along with cracks on the lips and a tendency to scaling. Riboflavin (4 mg daily) was given with a very gradual improvement. Because it was thought that the roughening of the skin might be the result of vitamin A deficiency, he was given percomorph oil (3 capsules daily) beginning in his third week. The vitamin A level in the blood was determined somewhat later and reported as normal, but there was never any change in the skin. His cevitamic acid intake was always adequate.

After the second month had passed, improvement became steady, continuing until discharge on 11/27/40. At this time, he weighed 43.6 kg, which was a gain of 11.3 kg over his low point reached at the end of his first month and one half, but only 3.6 kg more than his weight on admission. He felt well, had a good appetite, was cooperative and cheerful, and appeared to have regained his interest in life. His urinary output and thirst were well controlled by four pinches of posterior pituitary powder, taken as snuff, daily. The discharge diagnosis was anorexia nervosa, diabetes insipidus, and multiple vitamin deficiencies.

The patient remained at home for a month and 17 days. Shortly after discharge, however, he began to vomit and to complain of an uneasy feeling in his stomach shortly after eating. He frequently felt weak and listless and had to be urged to get outdoors. Urinary output remained well controlled, and it was thought that he was finding it difficult to adjust to life at home. Finally, it became apparent that he was slipping backward, and on 1/14/41 he was readmitted for further study.

At the time of admission he weighed 41.7 kg. Physical examination was generally as before. However, he was even more listless than at the time of his first admission, and he complained of his vision. At first it was thought that he required new glasses, as his eyes had not been refracted for several years. Closer questioning brought

out the fact that while at home he had noted that he had difficulty in making out objects across the street, or in recognizing his friends until they were very close. Also he had found that writing was awkward because of apparent double vision and because the pencil would vanish from sight when in certain positions. Visual fields (fig. 2) done on the Bjerrum screen, revealed total loss of vision in the lower temporal quadrant on the left and nearly total loss in the same quadrant on the right. Closer examination of the optic discs showed slight pallor, especially of the temporal portions. Stereoscopic roentgenograms of the skull were repeated and compared carefully with films taken in August and October, 1940. No evidence of any abnormality of the sella turcica could be found. The only possible abnormality noted was a doubtful backward displacement of the pineal gland.

Lumbar puncture yielded clear fluid under normal pressure and no evidence of block. Eighty-nine cells per

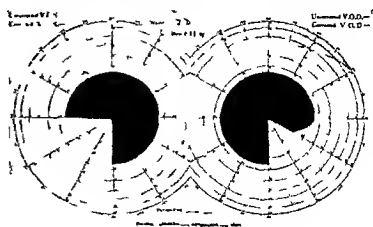


FIG. 2. CASE 1. VISUAL FIELDS.

cu mm, 50 per cent of which were polymorphonuclears, were found. Total protein was 112 mg per cent. It was thought that the patient had a suprasellar tumor, probably a craniopharyngioma, and he was transferred to the Neurosurgical Service of the Boston City Hospital for treatment. It was noted before transfer that the diabetes insipidus was less severe than previously, required less posterior pituitary powder for control, and that he occasionally had a rise in temperature to 99° or 99.6° F without evident reason.

He remained at the Boston City Hospital from 2/12/41 to 4/9/41. Because of his poor condition, surgery was withheld. Despite all efforts, he lost weight steadily and remained completely lethargic. Visual fields were checked frequently and remained the same except for the addition of a lower right nasal quadrant field defect. Roentgenograms of the skull showed the pineal gland displaced to the right and slightly posteriorly. An insulin tolerance test with 3 U of regular insulin intravenously gave values in mg per 100 cc: fasting, 85; 20 minutes, 62; 30 minutes, 60; 45 minutes, 71; 60 minutes, 72; 90 minutes, 87; 120 minutes, 86. Urinary 17 ketosteroids were 2.5 mg per 24 hours. Other laboratory data were the same as previously.

As he was considered too poor a risk for surgery, he was returned to this hospital on 4/9/41, at which time he weighed 32.1 kg. During the first week he gained 2 to 3 kg, but soon began to lose once more. During the third week vomiting became troublesome and at times almost

On this regimen he held his weight, gained in strength and planned to return to work. Following discharge he was seen regularly for 6 weeks during which period he gained weight and showed no more than minimal ankle edema at any time. Then he returned to Florida.

During the fall and winter his strength failed despite weekly injections of desoxycorticosterone acetate and 6 gm. of NaCl daily. He became lethargic and despondent. By March, 1941, his appetite had become very poor, and he began to vomit occasionally. Two weeks before his final admission on 4/8/41 he omitted the NaCl because

duction of salt and discontinuance of desoxycorticosterone acetate injections and of thyroid led to improvement. When thyroid was readministered, 10 days later, further vomiting resulted, so that it was stopped permanently. Whether there was any change in metabolic rate as a result of this medication cannot be stated, as a determination was not made after thyroid was started.

Eventually it became apparent that desoxycorticosterone acetate and salt were not adequate therapy. A trial was then made of suprarenal cortical extract with apparently good results. After a larger supply was obtained,

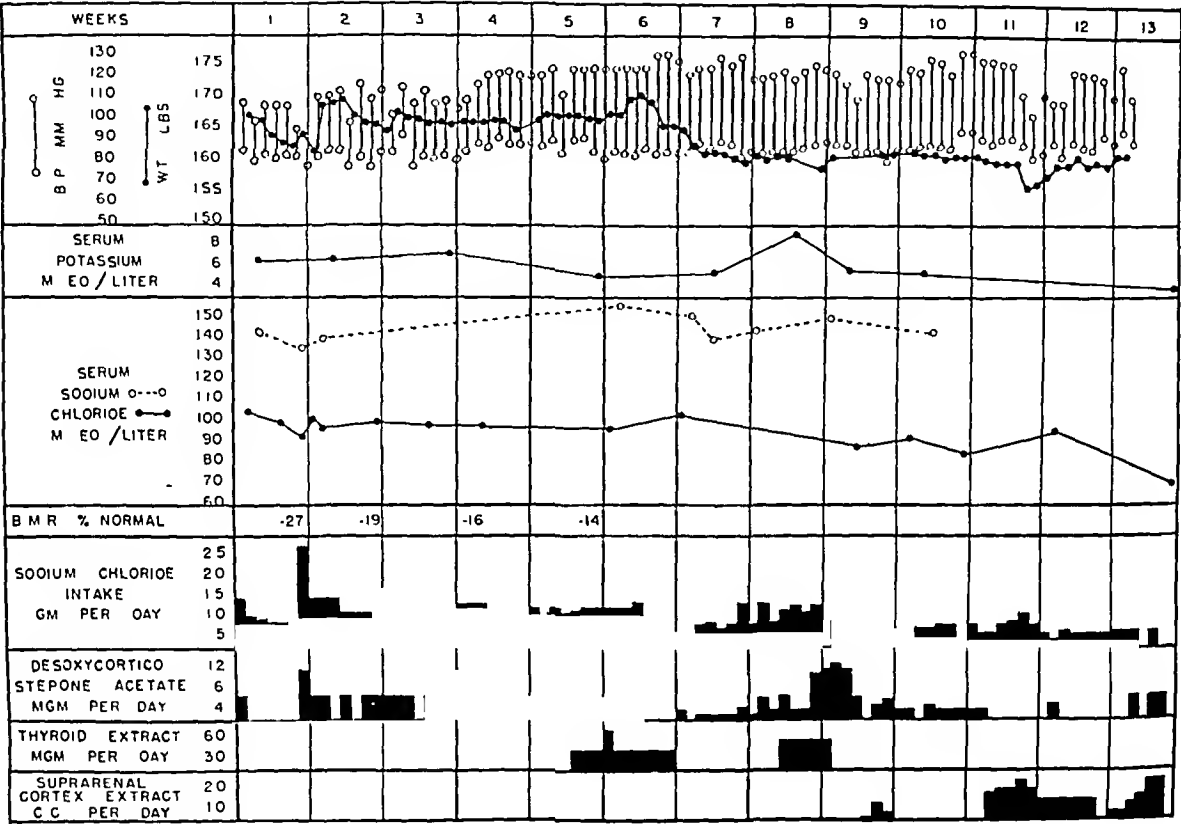


FIG. 4. Case 2. SUMMARY OF THE CLINICAL AND LABORATORY RESPONSE TO TREATMENT.

of anorexia, nausea and vomiting. As he continued to fail he decided to return to this hospital for further study.

Physical examination on readmission showed no significant change. There was moderate pitting edema of the legs, and the blood pressure was 104/68 mm. Hg. His course until death was quite variable. As is shown in figure 4, his weight tended to fluctuate roughly according to his NaCl and desoxycorticosterone acetate intake. For a time he gradually improved; his blood pressure was fairly well maintained, and he was able to be up and about. However, he had occasional vomiting episodes and was quite frequently bothered by a dull headache. During his second month in the hospital he was given a trial of thyroid extract, because he had felt better, in the past while taking thyroid. After 7 days he developed pleuritic pain on the left and showed signs of fluid, confirmed by x-ray. At this time, he also had peripheral edema and a higher blood pressure than at almost any other time. Re-

this was administered as shown in figure 4, in place of desoxycorticosterone acetate. Nevertheless, the patient failed steadily, eventually lapsing into coma and dying.

**Necropsy.** (Performed 1 hour and 25 minutes after death). **Brain.** Other than a moderate amount of arteriosclerosis, the brain showed no significant pathology.

**Pituitary.** The sella turcica was enlarged anteroposteriorly and laterally. Both posterior clinoid processes and the base of the sella were eroded and friable. The pituitary gland bulged from the sella, impinging on the posterior aspect of the optic chiasm. The gland was very soft and presented, on sectioning, a bulging, moist pale pinkish-gray surface, upon which no gross nodule could be discerned.

Microscopic study revealed an encapsulated nodule composed of sheets of normal-appearing chromophobe cells subdivided into lobules by a fine, vascular stroma, that comprised most of the gland. About the periphery was a

narrow, incomplete ring of compressed pituitary tissue, consisting of chromophobe, rare eosinophilic, and very rare basophilic cells. The pars intermedia contained a few cystic spaces lined with flattened epithelium and filled with colloid material. The posterior lobe was compressed, but was not otherwise remarkable.

**Thyroid.** Weight, 15 gm. This was soft and slightly smaller than usual. Sections showed the acini relatively uniform with completely involuted lining epithelium and filled with colloid.

**Adrenals.** Total weight, 15 gm. They were firm, smooth, and regular in outline, but somewhat reduced in size. No gross abnormality was noted on cut section. Microscopic examination showed the cortex well supplied with lipid and small foci in which the cortical cells were disintegrating and being invaded with lymphocytes, endothelial cells, and rare neutrophils. The medulla was not remarkable.

**Pancreas.** Weight, 60 gm. Grossly and microscopically this gland was not remarkable.

**Genitalia.** There was little of note grossly. Microscopically, the testes showed complete aspermatogenesis. The cells of the tubules were in various stages of disintegration, and the lumen of the tubules was more or less filled with amorphous, acidophilic debris. The interstitial tissue was edematous with slight cellular infiltration.

**Heart.** Hypertrophy was obvious and there was moderate coronary sclerosis.

**Lungs.** Bronchopneumonia, fibrocascous tuberculosis, and healed pleuritis were present bilaterally.

The final diagnoses were Chromophobe adenoma of the anterior lobe of the pituitary with pressure atrophy of both anterior and posterior lobes; complete involution of the thyroid, atrophy and focal necrosis of the adrenal cortices, senile atrophy of the testes, bronchopneumonia and fibrocascous tuberculosis, myocardial hypertrophy with moderate coronary sclerosis.

#### DISCUSSION

It seemed evident during prolonged observation that Case 1 represented a characteristic example of anorexia nervosa. He presented the emaciation, weakness, and low metabolic rate generally seen in anorexia nervosa, and probably had loss of sexual drive, as he appeared to have ceased to masturbate. Against this view was his lack of the restless drive which seems typical of functional anorexia (3), but his past history suggested that behavior abnormalities were to be expected. The improvement accompanying control of his diabetes insipidus and inception of a supervised regimen was thought to confirm the diagnosis of anorexia nervosa. Finally, the onset of definite visual changes indicated that an expanding intracranial lesion was behind all his symptoms.

The absence of calcification in the cranio-pharyngioma made early detection impossible. Unfortunately, this tumor belonged among the 20 per cent that, according to Cushing (8), fail to show detectable supra or intrasellar calcification. To judge

from the location of the tumor, the disturbed water-balance was the result of encroachment upon the supraopticohypophysial tracts. This would be consistent with the work of Fisher, Ingram, and Ranson (9) which showed that only lesions that destroy the posterior lobe of the hypophysis or the supraoptic nuclei or interrupt the neural pathways between the former and the latter result in diabetes insipidus. This syndrome occurred at some time in 15 per cent of the 101 verified cases of Simmonds' disease reviewed by Escamilla and Lissner (1). Whether the severity of the diabetes insipidus lessened as the anterior pituitary failed is not shown by their data. From the work of Ranson et al (9), however, this must have been so, as they found that destruction of the anterior pituitary in animals with experimental diabetes insipidus resulted in cure of the latter condition. Likewise, it has long been recognized that total hypophysectomy does not lead to diabetes insipidus, the suggested explanation (9) being that the anterior pituitary exerts a total diuretic influence without which the loss of the anti-diuretic principle of the posterior pituitary can exert no detectable effect upon fluid balance. In this connection it is interesting to note that the diabetes insipidus of Case 1 appeared to decrease in severity as anterior hypophysial failure became more pronounced.

The failure of pathologic examination of Case 1 to reveal unquestionable evidence of anterior pituitary damage might be considered to disprove the diagnosis of Simmonds' disease. Escamilla and Lissner (1) reviewed 14 cases that were clinically typical but showed normal pituitaries. Although they did not include them among their proved cases, they suggested that 6 had definite pathology in such close proximity to the anterior lobe that interference with its function was readily conceivable. An attempt was made to prove the diagnosis of Simmonds' disease by the use of the insulin tolerance test and the urinary 17-ketosteroid assay, as advocated by Fraser and Smith (10). The first test showed only a slight fall in blood sugar, only suggestive evidence of hypoglycemia unresponsiveness, and a return to the fasting level at 90 minutes. The second test gave a low value—2.5 mg. per 24 hours—but not the zero value (under 1 mg. per 24 hours) stated (10) to be characteristic of Simmonds' disease.

Despite the facts cited, the clinical course and non-pituitary necropsy findings in this case were so consistent with those shown by unmistakable instances of anterior pituitary failure that little doubt was permissible that this boy's pituitary had ceased to function significantly.

Case 2 offered no such difficulty in diagnosis on the necropsy findings. His anterior pituitary had been massively destroyed by the growth of a chromophobe

adenoma. However, clinically the diagnosis was not clear for a long while, despite x-ray evidence of enlargement of the sella turcica with thinning of the dorsum. These changes were of slight degree and were considered of doubtful significance by the neurological consultant. Also, the patient's response to thyroid and adrenal cortical extract suggested that his adrenal cortices were primarily insufficient. The clinical response to the salt deprivation test seemed to support this view, as did the marked improvement following desoxycorticosterone acetate and salt therapy. Likewise, the appearance of the patient suggested myxedema rather than pituitary cachexia. It gradually became plain, of course, that the cortical insufficiency was secondary and that the positive response to salt deprivation was the type of response that caused Stephens (4) to advocate the test as a method of diagnosing anterior pituitary failure. The myxedematous appearance coincided with the findings of Sheehan (6) and Castleman and Hertz (7) in cases of Simmonds' disease.

#### SUMMARY

The clinical course and necropsy data in two cases of Simmonds' disease are presented.

One occurred in a boy of 18 who had a craniopharyngioma that resulted in diabetes insipidus and, finally, in signs consistent with anterior pituitary failure.

The other occurred in a man of 70 who suffered from a chromophobe adenoma.

The difficulties encountered in differentiating between anorexia nervosa and Simmonds' disease are stressed, as well as the confusion that may arise because of the predominance of signs and symptoms resulting from hypothyroidism and hypo-adrenocorticism secondary to anterior pituitary failure.

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# Acromegalic Gigantism without Cardiac Enlargement:

## Report of a Case

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ACROMEGALY is usually associated with skeletal overgrowth and splanchnomegaly. Most observers regard cardiac enlargement as an essential feature of the disease.

The causative factor in the production of enlargement of the heart has been variously ascribed to a), direct hormonal activity (1), b), degenerative changes in the arterial vascular system (2), c), compensatory hypertrophy in response to the ever increasing demands of disproportionately rapid overgrowth of the body (3), and d), to alteration in the shape of the cavity of the chest (4).

Cameron (5) stated that the organs enlarge, especially the heart Cecil (6), Goldzieher (7), Mac Callum (8), Sternberg (9), Marie and Souza Leite (10), and others, believed that the heart participates in the general somatic and visceral enlargement. Englebach (11) stated that 'the heart is enlarged proportionately to the body growth.'

Hinsdale (2) described the changes in the heart as a true sclerotic myocarditis. Pathological studies by Cushing and Davidoff (12) have shown an increase in the amount of muscle fibers and supporting connective tissue, the enlargement being a concentric hypertrophy. In one of their cases the heart weighed 480 gm., but it seemed small in considering the size of the chest. Case IV of their series was a 21-year old woman with advancing acromegaly. The heart weighed 460 gm. In two others of their series, the hearts weighed 1000 and 1050 gm., respectively. Osborne (13) reported a case of acromegaly in which the heart weighed 1275 gm.

The extent to which the heart participates in the morbid changes of acromegaly is recognized by the frequent occurrence, in these cases, of a true cardiac syndrome. There is dyspnea, cyanosis, general weakness, and syncope. As the disease progresses, there is edema and albuminuria. Death usually occurs at an early age from heart failure.

The following case is of interest because the heart is not involved in spite of a well established and marked degree of acromegaly.

### CASE REPORT

The patient is a 34 year old male who began to show excessive growth at the age of eight. By the time he was 16 years of age he had attained almost his present height. At an early age he experienced intractable headache, progressive impairment of vision and weakness. Elsewhere he had been given a course of radiation to the pituitary gland which resulted in symptomatic relief. The amount of growth after the age of 16 is not definitely known, but it appears to have been relatively slight.

Physical findings of greatest interest were his physical proportions. He was 228.6 cm (7 ft, 6½ in) tall and had a span of 236.2 cm (92 in). His weight was 163.3 kg (359 lb). His chest circumference was 119.0 cm (46.4 in).

Examination of the heart and lungs revealed no significant abnormality. The heart rate was 60 per minute and the blood pressure 149/90 mm Hg.

Röntgenological examination showed the typical acromegalic changes in the skull (fig. 1). The bones showed enlarged trabeculae. There was expansion of the diploic table and a marked hyperpneumatization of the paranasal sinuses and mastoid cells. The sella turcica measured 11 x 14 mm, its floor being somewhat depressed and irregular. There was a moderate degree of prognathism but very marked progynium.

The hands measured 25.4 cm (9.9 in) in length and showed the usual bony changes of acromegaly (fig. 3).

The thorax was of particular interest. Fluoroscopic examination revealed a cardiac rate of 60, with normal rhythm and amplitude of contractions. There was no abnormality of contour. The lungs were luminous and there was normal respiratory excursion of the diaphragm.

Measurement of the teleroentgenogram (fig. 2) showed the internal transverse diameter of the chest to be 36.0 cm, transverse diameter of the heart 12.0 cm, length 15.0 cm, cardiothoracic ratio 33 per cent, area 1177 sq cm.

Comparison of these cardiac measurements with tables of standard average measurements shows that the heart in this case is not only not enlarged, but much smaller



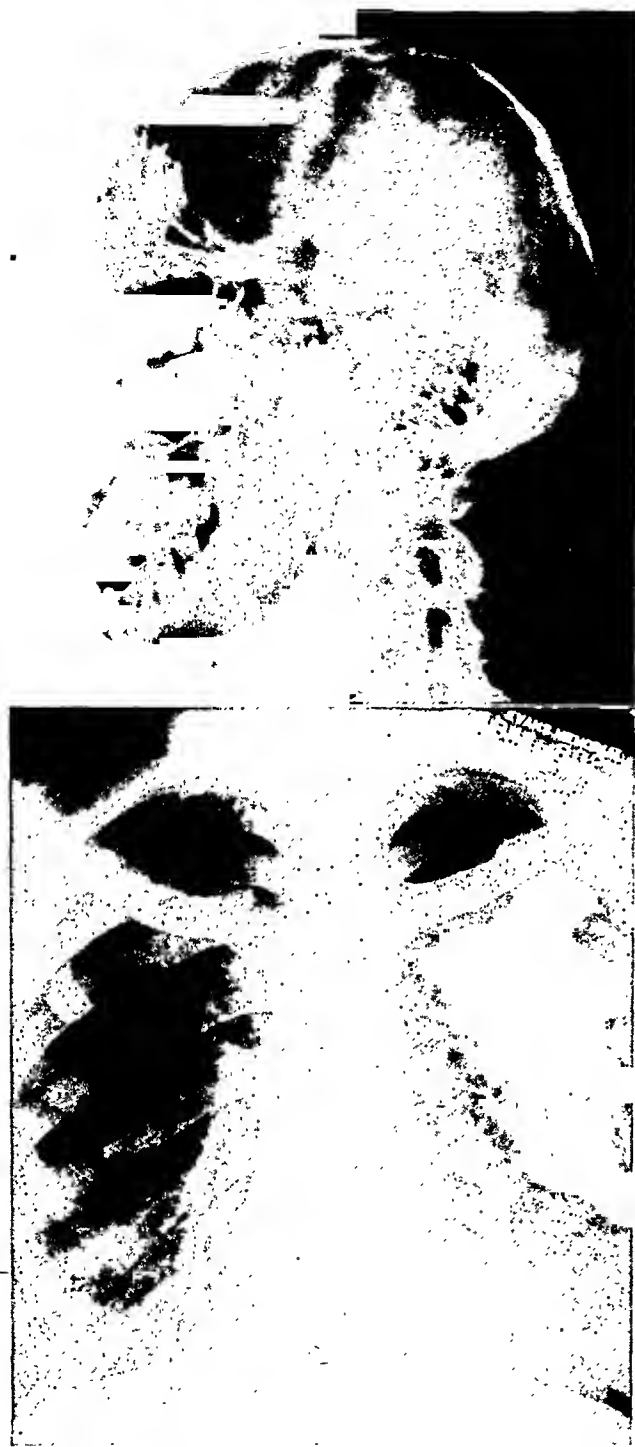


FIG. 1 (upper). SKULL SHOWING TYPICAL CHANGES OF ACROMEGALY. Note coarse texture of bone, expanded diploic table, marked hyperpneumatization of paranasal sinuses and mastoid cells, prognathism and progeneum. The sella turcica is enlarged and irregular. FIG. 2 (lower). TELEROENTGENOGRAM OF CHEST. Transverse diameter of lungs 36.0 cm.; transverse diameter of heart 12.0 cm.; cardio-thoracic ratio 33 per cent; length of heart 15.0 cm.; cardiac area 117.7 sq. cm. According to several standards, the heart is 56-66 per cent of the predicted normal value for a man of this size.

than the average normal for the size of the patient. The predicted cardiac area for the patient's height, weight, and age, based on the tables of Hodges and Eyster (14), is 188.07 sq. cm., while according to the tables of Claytor

and Merrill (15), his predicted area is 210.6 sq. cm. His actual cardiac area, obtained with a planimeter, was 117.7 sq. cm. This is only 62.1 per cent of the predicted normal area according to Hodges and Eyster's values and 56.0 per cent of Claytor and Merrill's.

According to Danzer's ratio (16), the transverse diameter of the heart in this case could be 18.0 cm. without being considered enlarged. Thus the transverse diameter is only 66.6 per cent of the predicted possible normal value. It is therefore of interest to check the size of the heart in this case according to other standards.

In previous studies, reported elsewhere (17), we have found the transverse diameter of the average normal heart to be 45 per cent of the pulmonary field. In this case of acromegaly the transverse diameter of the heart is 33 per cent of the transverse diameter of the pulmonary field. Accordingly, we find the heart to be only 64.4 per cent of the normal average value for a man this size. On the basis of the unscientific and empirical standard that 'a man's heart is as large as his clenched fist' we find such disparity between the size of the heart and the size of the hand, that, even though the roentgenogram was made with the hand extended, it is again obvious that the heart is small in this patient.

#### COMMENT

The absence of cardiac enlargement in this case appears to be of more than academic interest. Post-mortem studies by other observers (18) have shown cardiac enlargement to be an almost constant finding in the fatal cases. Moreover, the usual clinical picture includes a long period of cardiac insufficiency and ultimate failure. The patient presented in this report may be considered an arrested acromegalic giant. While his skin is extremely sallow, he presents no cyanosis, dyspnea, palpitation, edema or ascites. For many years associated with a well-known circus as a 'giant' he has, for the past two years, been engaged as sales promotion manager of a large business enterprise—a task equal to the efforts of any healthy and energetic businessman. His avocations are many and



FIG. 3. ROENTGENOGRAM OF HAND IN COMPARISON WITH THAT OF A NORMAL AVERAGE-SIZED ADULT.

varied so that his daily activities may be compared with those of any normal adult

That the heart was not enlarged in undoubtedly a factor in the better health enjoyed by this patient in comparison with most acromegalic giants. On the basis of tables of normal average measurements, we have reconstructed the patient to fit the size of the heart in this case and find that he should be 179 cm (5 ft. 9½ in.) tall, weigh 79 kg (174 lb.), and have an internal diameter of the chest of 26.6 cm. These changes are shown graphically in figure 4.

## SUMMARY

An unusual case of an acromegalic giant is presented, in which the heart is not enlarged. Comparison with several different standards shows the heart to be between 56 and 66 per cent of the predicted normal size for a man of his height, weight, and age.

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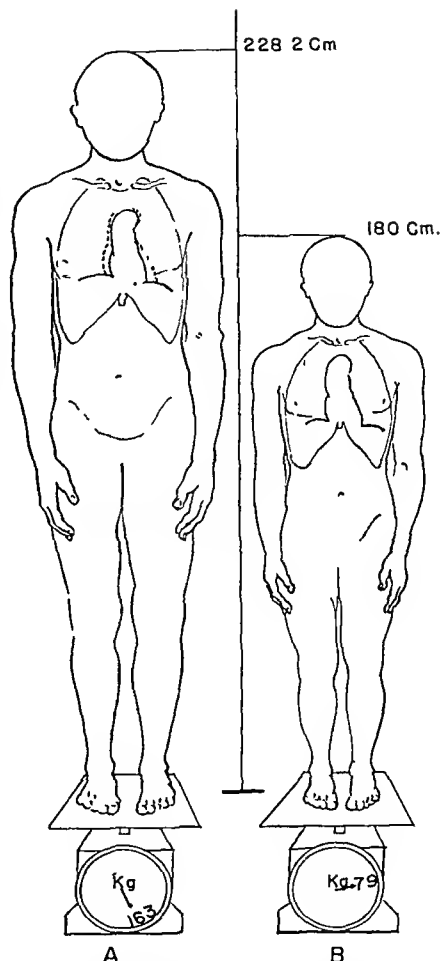


FIG 4. A. SCHEMATIC REPRESENTATION OF ACROMEGALIC GIANT and heart drawn to scale. Height, 228.6 cm (7 ft. 6½ in.), weight, 163.3 kg (359 lb.), pulmonary field 36.0 cm, transverse diameter of heart, 12.0 cm, length of heart, 15.0 cm. Dotted out line indicates size heart should be according to prediction tables. Transverse diameter of heart, 16.2 cm, length of heart, 18.6 cm. B. Man drawn in proportion to the size of the heart of the acromegalic giant. Height, 179.0 cm (5 ft. 9½ in.), weight, 79 kg (174 lb.), pulmonary field, 26.6 cm, transverse diameter of heart 12.0 cm, length of heart 15.0 cm.

# Observations on the Antagonistic Effects of Posterior Pituitary and Cortico-Adrenal Hormones in the Epileptic Subject<sup>1</sup>

[Epilepsy]

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PROGRESS in the development of a rational method of therapy for the so-called idiopathic form of epilepsy has been impeded greatly by our lack of exact knowledge concerning the nature of the peculiar physiological disturbance within the brain which is responsible for the spontaneous occurrence of generalized convulsions in afflicted persons. While gross or microscopic lesions undoubtedly occur in the cerebrum in many patients placed in this clinical category, they cannot be found in all, by any means. On the other hand, it has been observed repeatedly that not all persons exhibiting such brain lesions suffer from convulsions. Obviously, therefore, the immediate cause of the characteristic tendency to seizures should be sought in the realm of disturbances in cerebral physiology.

Recent developments in the use of the electroencephalograph (1, 2) for recording the electrical potentials of the brain (i.e., the so-called 'brain waves') have demonstrated beyond any question that the symptom which we recognize as an epileptic seizure is the outward manifestation of a profound disturbance in the electrical rhythm within the cerebral cortex. The different types of seizures (*grand mal*, *petit mal* and psychomotor variants) show different and highly characteristic brain wave forms. Presumably, the spontaneous development of abnormal electrical potentials on the surfaces of brain cells in certain foci is due to some underlying defect in cell membrane structure and function, or to some other factor interfering with the maintenance of normal relationships between the electrically charged elements within the brain. To determine the nature of such abnormalities and to find adequate means for their prevention or eradication is the primary purpose of scientific inves-

tigations in this field. The present preliminary report deals with one aspect of the problem.

Some years ago McQuarrie and Peeler (3) discovered that typical *grand mal* seizures could be induced almost at will in epileptic patients maintained on low-mineral dietaries by increasing their water intake and at the same time administering the anti-diuretic, posterior pituitary hormone (pituiratin or pitressin) at regular intervals in doses sufficiently large to prevent water diuresis. Non-epileptic control subjects showed no convulsive reaction to the procedure, although their general physiological response was the same. Since it has been shown that the absolute amount of sodium chloride excreted by the kidneys is increased during periods of pitressin anti-diuresis while water is being retained, it is obvious that the extracellular fluids of the body ultimately become diluted by this procedure, providing that the sodium chloride intake of the subject is kept below a certain level. Gilman and Barbour (4) demonstrated this directly by finding increased vapor tension of the blood serum of dogs under similar conditions. That dilution of the extracellular body fluids (or the accompanying disturbance in electrolyte balance brought about by the forced excretion of the Na and Cl ions) constitutes the essential provocative factor is indicated by the demonstration that seizures could not be induced in this manner if NaCl was administered during the period of the test in amounts sufficient to prevent such dilution. This conclusion regarding the rôle of body fluid dilution and associated disturbances in electrolyte relationships in the artificial induction of seizures was further confirmed by the clinical observations of Ziskin and Ziskin (5), who found it unnecessary to administer pitressin to obtain such results, if epileptic patients could be induced to drink water at the rate of 6 to 8 liters daily.

Since it has been demonstrated (6) that cortico-

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adrenal extract and synthetic desoxycorticosterone (7) produce effects on the water and mineral exchanges of the body, which are in many respects diametrically opposite to those of pitressin, it was thought desirable to determine the response of epileptic patients to these cortical hormones. Our objective in the present investigation was not only to ascertain the effectiveness of the adrenal cortical hormone in preventing the seizures, which would otherwise be expected to occur spontaneously, but also to determine how it might alter the patient's convulsive response to the pitressin antidiuresis test. Complete electrolyte and water balance studies, as well as serum electrolyte analyses, were carried out in the case of one severely epileptic adult patient who volunteered to serve as an experimental subject. A less elaborate trial was made, also, in the case of a 12-year-old epileptic boy.

The adult patient, R., aged 26 years, was an especially suitable subject for the investigation because he had an 18 year record of typical *grand mal* seizures, in some of which he had sustained such severe injuries as multiple fractures of the mandible, loss of teeth and lacerations of the tongue. Petit mal seizures likewise occurred at times, particularly during the earlier years of his illness. He was a highly intelligent, former college student, which fact made cooperation entirely satisfactory. Repeated neurological examinations, as well as pneumoencephalography and serological tests, made during the previous year by members of the Department of Neuropsychiatry, revealed no evidence of organic disease of the central nervous system. He gave the history of having responded fairly well to the ketogenic dietary regimen at an early age, but within recent years he had found that phenobarbital and mebarol were required in ever-increasing doses to prevent the occurrence of seizures at daily or even shorter intervals. This form of medication produced extreme sluggishness of his mental processes and slurring and excessive slowness in his speech, which made it impossible for him to secure employment. Unfortunately, dilantin in fairly large doses had failed to prevent his *grand mal* attacks, when given a trial several months prior to the beginning of the clinical investigation reported here.

During the week preceding his admission to the hospital for special study, the patient was requested to omit all medication in order that its effects might not influence the experimental results. Upon admission to the University Hospital on April 28, 1941, he was immediately placed on a standard, low mineral diet served in four equal meals at 6 hour intervals. He was maintained on this without modification until the time of his discharge. The total water intake amounted to 2600 cc daily. During a 4 day preliminary control period on this regimen without medica-

tion, he had three severe *grand mal* seizures, indicating that the effects of his previous barbiturate medication had largely worn off. Throughout the succeeding 13 days he was given desoxycorticosterone acetate<sup>2</sup> intramuscularly in doses of 5 mg every 6 hours. At the end of one week on this treatment, he was subjected to the pitressin test, receiving 0.5 cc of pitressin subcutaneously every 3 hours night and day while the administration of desoxycorticosterone acetate was continued. A control pitressin test was carried out 4 days after discontinuance of the desoxycorticosterone acetate treatment.

#### RESULTS

The results of the desoxycorticosterone-pitressin experiment and those of the control pitressin test are presented graphically in figure 1. As indicated on the chart, three spontaneous convulsions (C) were observed during the preliminary period before administration of desoxycorticosterone acetate was begun, whereas none occurred during the next 7 days. This freedom from convulsive attacks was tentatively interpreted as an indication that the desoxycorticosterone acetate exerted a protective influence against spontaneous epileptic seizures. An attempt to test the effect of this synthetic hormone on the occurrence of pitressin induced seizures was then made.

Near the end of the third day of pitressin administration, a moderately severe *grand mal* seizure occurred, within 2 hours after the patient had dutifully drunk 900 cc of water in a short period of time to make up the total intake prescribed for the day. Continuation of the desoxycorticosterone acetate for 36 hours after withdrawal of the pitressin greatly attenuated the post-pitressin diuresis and appeared to ameliorate the unpleasant aftermath of the convulsive attack. When the control pitressin test was performed 4 days following discontinuance of the desoxycorticosterone acetate, the patient began to have seizures within 12 hours, before he had had time to store a large amount of extra water. Since none of the three seizures occurred within an hour after administration of the antidiuretic agent, and so appear not to have been due to cerebral vascular effects, the interpretation of an internal shift in the water and electrolytes of the brain was assumed as a factor in the causation of the attacks. Seizures temporarily ceased to occur, as usual, soon after pitressin was withdrawn and the induced disturbances in water and electrolyte balances had disappeared.

Measurements of the daily intake and output of the various electrolytes during the course of the experiment showed distinctly greater retention of sodium and chloride during the period of treatment with

<sup>2</sup> The desoxycorticosterone acetate was supplied by the Schering Corporation, Bloomfield, N. J.

desoxycorticosterone acetate than during the preliminary control period. The potassium excretion, on the other hand, was increased by the desoxycorticosterone acetate during the first 4 days. As indicated by the body weight curve, water was initially retained with Na and Cl as a result of administration of desoxycorticosterone acetate. This response was followed shortly, however, by a diuresis which persisted until pitressin administration was begun. Con-

following omission of desoxycorticosterone acetate suggests a 'carry over' effect of the latter. During the following control pitressin-test period, however, the excretion of Na and of Cl was greatly increased, while K was retained in the body. These effects were, therefore, diametrically opposite those characteristically produced by desoxycorticosterone (7). Except for reduction in serum K, the blood electrolytes were unaltered.

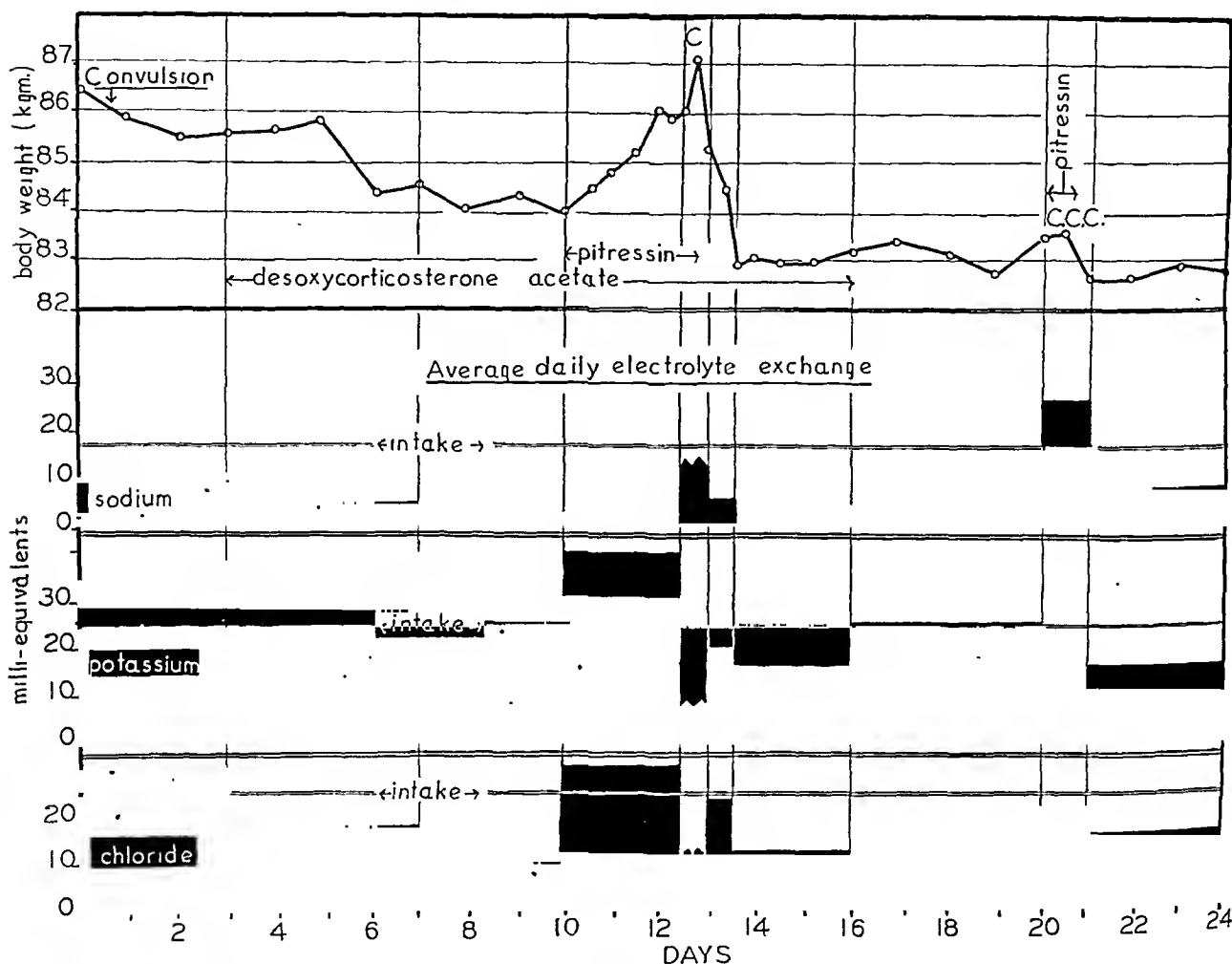


FIG. 1. ANTAGONISTIC EFFECT OF DESOXYCORTICOSTERONE ACETATE on the seizure-provoking action of pitressin in epileptic subject. Low mineral diet. 2600 cc. of water per diem. Columns in black represent average daily excretion of electrolytes in urine.

trary to expectation, the retention of Na was increased when pitressin was given in addition to desoxycorticosterone acetate. At the same time the excretion of K and that of Cl was increased. Exact data relating to the electrolyte excretion during the day following the seizure are not available because an undetermined amount of urine (one large voiding) was lost. The effect of desoxycorticosterone acetate on K excretion during the period of recovery from the pitressin experiment appears to have been modified by the latter, since it was much less during the 3 post-pitressin days than before. The retention of Cl and Na, as well as the freedom from seizures, for 4 days

Following completion of these short experiments, the patient was discharged from the hospital on an ordinary mixed diet with desoxycorticosterone acetate in sesame oil intramuscularly in doses of 10 mg. daily as the sole therapeutic agent. Because of reported untoward effects of too-long use of this synthetic hormone in large doses (8), the patient was examined at frequent intervals and the serum K was determined weekly.

The apparent result of this therapeutic trial was that he remained free from seizures for 46 days. The first seizure to occur after this comparatively long interval followed reduction of the dosage of desoxy-

corticosterone acetate to 5 mg daily. This reduction in dosage was considered desirable because the serum K was found to have decreased to 11 mg per 100 cc and the blood pressure had become elevated to 150 systolic and 112 mm Hg diastolic. Within a few days after withdrawal of the desoxycorticosterone acetate, however, these values returned to normal without immediate recurrence of seizures. The patient's mental reaction and his speech became essentially normal with cessation of seizures, so that he was able to hold an office position after leaving the hospital. Whether or not the mental sluggishness and 'thickness' of speech which was present until the desoxycorticosterone acetate was given were due entirely to the previous barbiturate medication, to the effect of seizures, or was associated with the primary brain cell abnormality is problematical. Since withdrawal of the desoxycorticosterone acetate in August, 1941, the patient has remained almost entirely free from seizures by restricting his water intake sufficiently to maintain the specific gravity at or near 1.030. No medication has been given.

A second severely epileptic patient, E.R., aged 12 years, when subjected to similar experiments with desoxycorticosterone acetate, likewise showed a decided prolongation of the time required for induction of a *grand mal* seizure by means of pitressin antidiuresis and forced water drinking. Placed on treatment with desoxycorticosterone acetate in a dose of 5 mg daily and given an ordinary mixed diet, he remained seizure free while under our observation for more than 3 months, except for occasional *petit mal* attacks.

#### DISCUSSION

It is apparent from these preliminary observations that desoxycorticosterone acetate exerts a protective effect against the induction of *grand mal* attacks in the epileptic subject by means of pitressin antidiuresis and forced water drinking. Spontaneously occurring seizures of the *grand mal* type also appear to be lessened in number or prevented entirely by this hormone under certain conditions. *Petit mal* seizures may not be affected to the same extent. The general effects of desoxycorticosterone acetate on the water and electrolyte exchanges of the body are the same in the epileptic as in the normal subject. The specific action of the hormone in causing retention of Na and Cl in the extracellular body fluid, thereby tending to prevent dilution of the latter, appears to be crucial. Increased excretion of water is likewise important, except when excessive amounts of pitressin are given. We are now attempting to determine whether or not changing of the K content of the brain cells and serum plays an important part in reducing the convulsive tendency. While epileptic patients do not show any of the

ordinary signs of adrenal cortical or renal insufficiency, their abnormal convulsive response to increased water intake and forced pituitary antidiuresis resembles the increased sensitiveness of adrenalectomized animals to 'water intoxication' in which convulsions occur (9, 10, 11). Desoxycorticosterone (12) and other adrenal cortical steroids (13) have been shown to protect the latter animals against 'water intoxication,' just as desoxycorticosterone in the present investigation was shown to protect our epileptic patients from the convulsive effects of forced dilution of the extracellular body fluids.

Whether or not other cortical hormones would be so effective as desoxycorticosterone acetate in protecting the epileptic subject against spontaneous or pitressin induced seizures cannot be said until comparative tests have been carried out. It may be mentioned in passing, however, that we observed some protective effect against spontaneously occurring *grand mal* attacks in one severely epileptic patient in 1935, when a whole cortical extract (kindly furnished by Dr. E. C. Kendall) was administered at regular intervals. The finding by Eversole, Gaunt and Kendall (13) that Kendall's compound E (17-hydroxy-11 dehydrocorticosterone) was greatly superior to desoxycorticosterone acetate in protecting adrenalectomized rats against the effects of excess water intake suggests that this substance should be given a trial in epileptic subjects when it becomes available in sufficient quantity for that purpose.

The anticonvulsive effect of dehydration frequently observed in epileptic patients subjected to severe water restriction (14, 15), diuresis or catharsis (16) appears to the present authors to be due to its influence on the electrolyte relationships in the various fluid compartments of the central nervous system. By proper adjustments of the dosage of desoxycorticosterone acetate (or other cortico-adrenal steroids) and the intake of water, K, Na and Cl, an improved method of therapy might be developed to effect the same end in a physiological, as well as a much more tolerable, manner. In the present state of our knowledge, however, this form of therapy cannot be recommended for general use. Additional physiological and clinical studies are in progress.

#### SUMMARY

1. The effects of desoxycorticosterone acetate on the water and electrolyte exchanges and on the occurrence of *grand mal* seizures was determined in two severely epileptic patients.

2. It was found that this synthetic cortical adrenal hormone effectively antagonized not only the electrolyte responses, but also, under the conditions represented in these experiments, the seizure-provoking

effect of the antidiuretic posterior pituitary hormone (pitressin).

3. Preliminary therapeutic tests indicated that desoxycorticosterone decreases the tendency to spontaneous occurrence of *grand mal* seizures, also.

4. The probable mechanism of this action is discussed.

5. The results presented tended to confirm our earlier conclusion regarding the nature of the convulsive mechanism in genuine epilepsy.

6. Possible dangers from prolonged, indiscriminate administration of desoxycorticosterone acetate contra-indicate its use until further investigations now in progress have been completed.

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# Addisonian Crisis Complicated by Relative Hypertension, Edema, and Acute Streptococcus Hemolyticus Infection of the Throat

## [Addison's Disease]

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THE PROGRESS in the treatment of Addison's disease received considerable impetus with the synthetic preparation of desoxycorticosterone acetate by Steiger and Reichstein (1). Clinical reports began to appear attesting to its efficacy in this disease (2-5) and, indeed, the enthusiasm manifested in these reports was well merited. The patients in Addisonian crisis responded satisfactorily and the distortion in the blood electrolyte pattern so characteristic of the crisis was promptly corrected. However, toxic manifestations, such as hypertension, edema, and heart failure resulting from overdosage with the drug were observed (4, 5).

We have under our observation a patient with Addison's disease who developed acute adrenal insufficiency while under treatment with desoxycorticosterone acetate. The crisis was complicated, and perhaps even precipitated by a hemolytic streptococcal tonsillitis. The picture was unusual in that the adrenal insufficiency occurred while the patient had a relative hypertension and diffuse edema. Treatment with large doses of cortical extract, intravenous fluids, and sulfadiazine resulted in recovery. Recently, Thorn and Lewis (6) reported the successful treatment of two patients with Addison's disease who developed acute hemolytic streptococcal tonsillitis. They commented upon the necessity of supplementary treatment with cortical extract in addition to the use of desoxycorticosterone acetate, sulfadiazine and intravenous fluids.

### CASE REPORT

The patient is a 59-year old white Russian housewife, who had been ill for 8 years preceding the present admission to the hospital. During this period she had fre-

quent episodes of abdominal distress and vomiting. Five years ago her blood pressure was noted to be low. Approximately one year ago she was admitted to the Mount Sinai Hospital for study. At the time of admission she complained of marked weakness, loss of 25 pounds in weight, anorexia, nausea and vomiting, and darkening of the skin. Upon investigation, the blood pressure was found to be 60/40 mm Hg. She had typical Addisonian pigmentation, and abdominal roentgen ray studies revealed extensive calcification in the regions of the adrenal glands. The blood sodium at the time of admission was 123.4 m eq per liter, the chlorides 94 m eq per liter. The urea N was 21 mg per cent. She was markedly dehydrated. Treatment was started with intravenous isotonic saline, injections of desoxycorticosterone acetate intramuscularly, and the administration of salt by mouth. There followed a prompt remission of the symptoms with a return of the blood sodium and chloride concentration to normal levels, and an increase in the blood pressure to 110/70 mm Hg. She was then maintained with daily intramuscular injections of 1 to 2.5 mg of desoxycorticosterone acetate, plus 6 gm of supplementary salt by mouth. On this regimen she felt well, and the blood pressure, weight and blood sodium concentration were maintained within normal limits.

One week before the present admission to the hospital, the patient noted slight puffiness of the face and edema of the ankles, and her family physician found her blood pressure to be 140/90 mm Hg. She complained of weakness, anorexia, and some nausea. She omitted one injection of desoxycorticosterone acetate, but the next day resumed injections of 1 mg of the drug plus the 6 gm of salt by mouth. During the course of the next 2 or 3 days the ankle edema subsided, although the puffiness of the face persisted. Two days before admission to the hospital the blood pressure was 130/80 mm Hg, but the asthenia and nausea were more pronounced. The blood sodium was 123 m eq per liter and the chlorides 94 m eq per liter. It was evident that despite the relative increase in blood pressure and the edema that the patient was developing adrenal insufficiency.

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<sup>1</sup> Charles Klingenstein Fellow.



Upon admission to the hospital the patient appeared acutely ill. She complained of marked weakness and nausea, although no vomiting had ensued. There was moderate edema of the face and eye lids. The blood pressure was 150/90 mm. Hg, the blood sodium was 116 m.eq. per liter, the chlorides 78 m.eq. per liter. The urea N was 10 mg. per cent, while the serum proteins were 6.3 gm. per cent. The hematocrit was 30, the hemoglobin was 77 per cent, and the white blood cell count was 4800 with a normal differential. The examination of the urine was negative. At this time no evidence of pharyngitis or tonsillitis was observed. Four hours after the hospital admission the patient began to vomit and the blood pressure fell to 110/70 mm. Hg. It was now obvious that she was in severe adrenal insufficiency despite the presence of

Two days after the hospital admission her temperature rose suddenly to 103° and the next day to 105.4° F. Examination at this time revealed a markedly injected and edematous pharynx with startling swelling of the tonsils. Hemolytic streptococci in large numbers were cultured from the throat. Concomitant with the febrile reaction there occurred a drop in the blood pressure to 95/60 mm. Hg, and a pronounced fall in the blood sodium to 116 m. eq. per liter. The adrenal cortical extract was increased to 50 cc. a day, of which 30 cc. as well as an initial dose of 4 gm. of sodium sulfadiazine followed by 1 gm. every 4 hours, were administered intravenously. In addition, the constant intravenous infusion of 5 per cent glucose in isotonic saline was continued. During this two-day period, the patient appeared desperately ill. The temperature

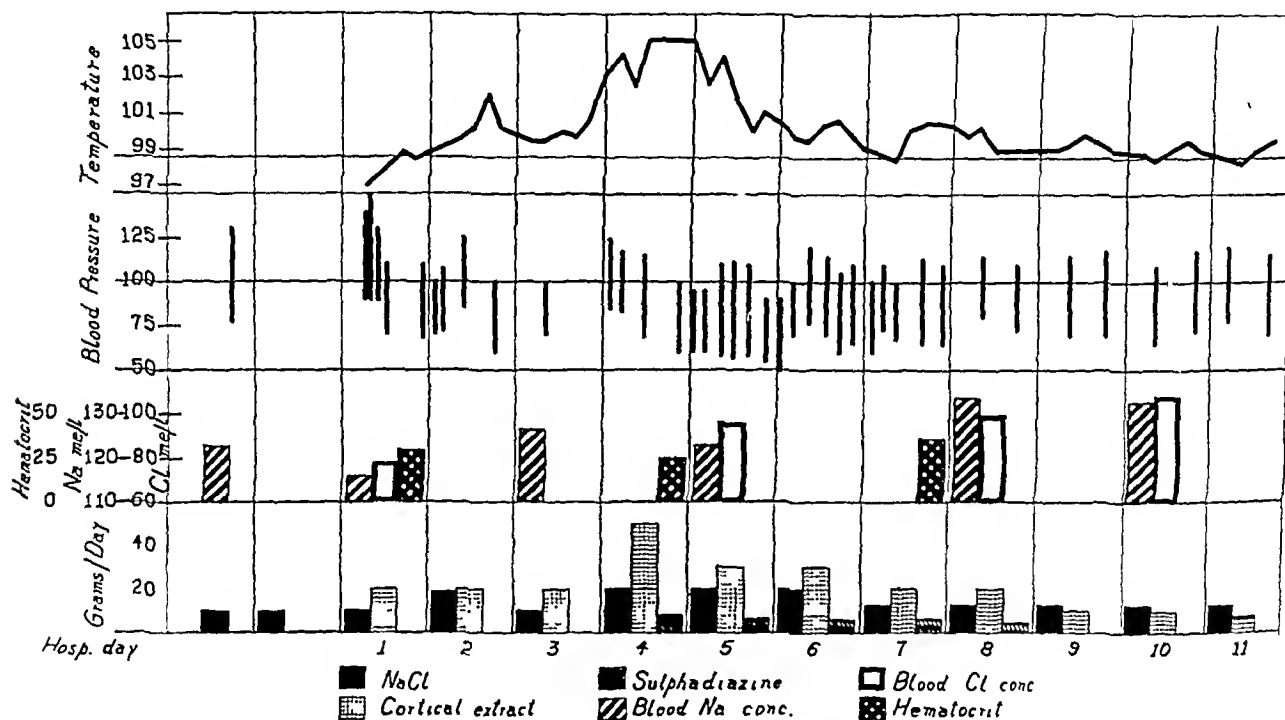


FIG. 1. SUMMARY OF CASE.

edema, a low hematocrit, and normal or slightly elevated blood pressure. In view of these phenomena it was felt advisable to change from desoxycorticosterone acetate to adrenal cortical extract. Accordingly, she was given 20 cc. of extract<sup>2</sup> intravenously and 10 cc. twice a day subcutaneously. In addition, a constant intravenous infusion of 5 per cent glucose in isotonic saline was given. The following morning there was considerable improvement and the blood pressure varied between 125/84 and 100/70 mm. Hg. The same regimen, however, was continued, and 36 hours after the intensive therapy was instituted she felt quite well. The blood sodium was 126.8 m.eq. per liter and the chlorides 95 m.eq. per liter. It is interesting to note that despite the administration of 2800 cc. of fluids intravenously the edema had subsided.

remained at 105° F., and she was completely disoriented. On the morning of the third day, the temperature fell precipitately to 100° F., and from this point on recovery was fairly rapid. When recovery was well advanced, the intravenous medication and fluids were discontinued and the amount of adrenal cortical extract given subcutaneously was gradually reduced to 4 cc. per day. In addition, she now received 8 gm. of salt orally. The sulfadiazine in doses of 1 gm. every 4 hours was continued for 3 days after the temperature returned to normal levels. Ten days after admission, the patient was perfectly well; the blood sodium and chlorides were 132.9 m.eq. per liter and 102 m.eq. per liter, respectively, and the blood pressure was 120/80 mm. Hg.

#### DISCUSSION

The asthenia, nausea, vomiting, and low concentration of blood sodium and chloride on hospital ad-

<sup>2</sup> The cortical extract was supplied by The Upjohn Co., Kalamazoo, Mich.

mission were indisputable evidence of a severe Addisonian crisis in a patient with known Addison's disease. The clinical and chemical picture was unusual in that she had neither hypotension, hemoconcentration, azotemia, nor dehydration. This dissociation of the individual manifestations of adrenal insufficiency would further support the concept that more than one hormone is concerned with the regulation of adrenal cortical function. This has its clinical corollary in the recognition that desoxycorticosterone does not by any means represent complete replacement therapy. It has been noted repeatedly (3, 5, 7, 8) that this compound exercises little effect on the disturbance in carbohydrate metabolism in Addison's disease. That other functions of the adrenal cortex may not be possessed by desoxycorticosterone is suggested by the work of Ingle (9) who showed that it did not exert as potent an effect on the muscle work capacity of adrenalectomized rats as some of the other crystalline factors. Finally, Britton and Kline (10) have pointed out that adrenalectomized cats in acute insufficiency respond more promptly and completely to adrenal cortical extract than to desoxycorticosterone acetate. It should be emphasized that desoxycorticosterone is an invaluable drug in the treatment of Addison's disease, but occasionally clinical circumstances arise which necessitate supplementary treatment with, or substitution of, whole adrenal cortical extract.

The development of acute upper respiratory infections has always been a serious complication in patients with Addison's disease. Such infections have usually been difficult to control and have usually been associated with high fever, poor leucocyte response, spreading infection, and the development of signs and symptoms of acute adrenal crisis. With the advent of the newer and less toxic sulfonamide compounds and the intelligent use of the more potent cortical ex-

tracts, the lives of many of these patients can be saved.

#### SUMMARY

A case of Addison's disease is reported in which acute adrenal insufficiency occurred while under treatment with desoxycorticosterone acetate and in the presence of relative hypertension and edema. The problem was further complicated by the development of acute tonsillitis due to hemolytic streptococci. Recovery followed the administration of sulfadiazine, whole adrenal cortical extract, and intravenous fluids and transfusions.

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# Prevention of Diabetes Mellitus<sup>1</sup>

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IN THE LITERATURE on the prevention of diabetes one finds attention drawn to the fact that heredity, race, and obesity are among the important factors that influence the development of this disease. If one could choose a mate with no diabetic taint in the family and not develop obesity the incidence of diabetes could be appreciably reduced.

Strome and Blaine (1) point out that mortality rates from diabetes are higher in the United States than in any other major civilized country and that these are increasing every year.

In 1933 the author (2) suggested that if one could diagnose diabetes before it became clinically apparent and could treat the disturbance successfully a considerable step forward in reducing the incidence and mortality of this disease would be achieved.

The author has previously reported (3) that approximately 15 per cent of patients of college age having glycosuria on one examination would have some degree of disturbance of carbohydrate metabolism as judged by routine glucose tolerance tests. The present report deals with results of clinical studies and periodic glucose tolerance tests made on some 90 patients who had various degrees of disturbed glucose tolerance over a period of 9 years.

## CLASSIFICATION OF PATIENTS

Patients found to have disturbed glucose tolerance were placed in one of the following groups. *Group I, diminished tolerance.* The blood sugars were normal throughout the tolerance tests<sup>3</sup> except that the initial rise after ingestion of glucose was above 180 mg. per cent. *Group II, diminished assimilation.* Normal

fasting blood sugar and no blood sugar above 180 mg. per cent during the test, but a failure of the 2½-hour blood sugar to return to normal (120 mg per cent or below). *Group III, diminished tolerance and assimilation.* Normal fasting blood sugar (120 mg. per cent or below), and all other blood sugars during the test above normal. *Group IV, diabetes mellitus.* A) Chemical diabetes; all blood sugars above normal e.g., a typical diabetic glucose tolerance test, but no clinical symptoms of the disease B) Chemical findings the same as in previous group and, in addition, one or more clinical symptoms of the disease, such as polyuria, nocturia, increased thirst and fatigue.

## PROCEDURE

No patient was included in this study who had evidence of hyperthyroidism, infection, liver disease, or previous diagnosis of a disturbed glucose tolerance. Patients were classified into various groups on a basis of the results of the tolerance tests. During the first two years of the study individuals of comparable age, sex and tolerance were divided within each of the four groups. One half of these were placed on diets; the other half served as controls. Periodically these individuals were given glucose tolerance tests and were observed for signs and symptoms of diabetes. At the end of this time several things became apparent: a) Diabetes was not acute in its onset but was a very gradually developing disturbance that became progressively worse if not treated b) The difference in response between the treated and control patients in Groups I and II was not significant. During the rest of the period of study (1933-40) only those patients whose tolerance tests classified them in Groups III and IV were consistently followed by periodic observation, tolerance tests, and treatment

## TREATMENT

Therapy consisted of diet alone. The diet was of the restricted fat (approximately 56 gm.), low caloric type. The patient was placed on a diet of carbohydrate, 56, fat, 56, protein, 42, until the fasting blood sugar was below 120 mg. % and postprandial glyco-

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<sup>1</sup> Read before the twenty-fourth annual Meeting of the Association for the Study of Internal Secretions, June, 1940. Delay in publication of this article was deliberate. The method of preventing diabetes described herein was given to several clinics to try for a year in order to see what could be accomplished. So far the results have been gratifying and I believe a method for the prevention of diabetes has been established.

<sup>2</sup> Present address. Battle Creek Sanatorium, Battle Creek, Michigan.

<sup>3</sup> One hundred gm. of glucose in 250 cc. of water was used in all cases.

sunas disappeared, then 18 gm of carbohydrate and 3 gm of protein (approximately 1 slice of bread or its equivalent) was added (case 8). If postprandial glycosuria appeared, the patient was kept at this dietary level until the urine was sugar-free and again the same amount of carbohydrate and protein was added. The diet was gradually built up to maintenance by this procedure. If glycosuria appeared constantly after any single increase, the diet was reduced to the previous level and maintained there until the glycosuria disappeared. The diet was then increased in amounts of 9 gm of carbohydrate and 1.5 gm of protein instead of 18 and 3 gm, respectively.

In all but a few instances weight,<sup>4</sup> health, and activity could be maintained by keeping the fat at a low level as carbohydrate and protein were added. In several instances, however, it was necessary to increase the fat content of the diet to 10 or 15 gm when the carbohydrate tolerance was short of a maintenance diet, and further increase of carbohydrate was not tolerated.

#### DISCUSSION

The development of clinical diabetes divided itself into several stages: a, diminished tolerance or diminished assimilation; b, diminished tolerance and assimilation; c, chemical diabetes; d, clinical diabetes (cases 1-4). The onset of clinical diabetes, while it may appear to be acute, is in most instances preceded, for weeks or months, by changes in the blood sugar values which gradually become more severe (case 1).

In this study it was amazing to see how greatly disturbed the glucose tolerance could be and yet not produce clinical symptoms and, conversely, to note that mild disturbances in glucose tolerance in some instances produced clinical symptoms which were quite marked (case 5, 6). The question of why this occurs is as yet unanswered.

The problem of when to begin dietary treatment of a disturbed glucose tolerance is difficult. The findings in this study show that excellent results are obtained when individuals having a diminished tolerance and assimilation, or chemical diabetes are treated. Those individuals in the early stages of chemical diabetes respond favorably to diet (case 1, 6, 7, 9). The longer these patients remain untreated and the more symptoms of clinical diabetes that develop, the poorer the prognosis for recovery (case 2, 10).

The author does not believe that treatment should be instigated when an individual is classified in Groups I and II. Patients of the type in Groups III and IV should be treated, if the incidence of clinical diabetes is to be reduced. Insulin is not necessary unless clinical diabetes or acidosis are present.

<sup>4</sup> Five to 10 per cent under ideal weight as calculated by standard height weight tables.

as, in the author's experience, it has been found to retard recovery in early disturbances in tolerance.

The problem of how long the recovered patient should be kept on a diet is difficult. It seems safe to assume that the diet should be followed for a period of at least one year after recovery and then the patient should be warned to maintain the state of mild under-nutrition attained at the time of cessation of the diet. In fully recovered patients, no return of elevated blood sugars or clinical symptoms of diabetes have

TABLE 1 RESULTS OF GLUCOSE TOLERANCE TESTS AT THE BEGINNING AND END OF THE DIET PERIOD

|   | Fasting | ½ hour | 1 hour | 2 hours | 2½ hours |
|---|---------|--------|--------|---------|----------|
| Mean blood sugar when diet began mg %       | 113     | 188    | 220    | 205     | 179      |
| Mean blood sugar at end of diet period mg % | 102     | 152    | 152    | 132     | 107      |

been noted when this suggestion has been carefully followed.

No explanation as yet can be offered as to why recovery takes place on this regime. Reduction of weight alone was not responsible, as most of the patients were not obese when first seen and they were of practically the same weight at the end of the dietary period as they were at its beginning. That obesity is not an uncommon finding associated with a disturbed glucose tolerance in the older age group is recognized. Twenty-one per cent of these patients with disturbed glucose tolerance had family history of diabetes.

The fact that a normal fasting blood sugar is not a safe index of the severity of the disturbance present is demonstrated (case 7, 11). In considering the significance of an elevated fasting blood sugar in the absence of postprandial glycosuria, the possibility of a high renal threshold for glucose should always be considered (case 2, 3, 6, 8). During this study it was repeatedly demonstrated that the renal threshold may vary in the same individual on different occasions (case 7).

The fact that clinical diabetes can actually be prevented is demonstrated by cases 1, 2, 6, 7, 9, 10, 11 and 12. Cases 3 and 4 are examples of what one sees in those cases which served as controls and were untreated. Table 1 shows the mean bloodsugar values of glucose tolerance tests at the beginning and end of the diet period.

These clinical studies indicate that, by the use of glucose tolerance tests, it is possible to make an early diagnosis of a disturbed carbohydrate metabolism.

CASE PROTOCOLS

CASE 1

R. D., male, age 21; referred because of a marked glycosuria. No symptoms of diabetes.

|          | 12/21/32          |                   | 2/26/34 |      | 5/15/34              |      | 6/20/34        |      | 9/24/34   |      | 2/1/35                                      |      | 4/2/35               |      | 7/2/35   |      | 10/11/35              |      |
|----------|-------------------|-------------------|---------|------|----------------------|------|----------------|------|---|------|---|------|----------------------|------|----------|------|-----------------------|------|
|          | B.S. <sup>1</sup> | U.S. <sup>2</sup> | B.S.    | U.S. | B.S.                 | U.S. | B.S.           | U.S. | B.S.  | U.S. | B.S.  | U.S. | B.S.                 | U.S. | B.S.     | U.S. | B.S.                  | U.S. |
|          | No diet           |                   | No diet |      | No diet              |      | No diet        |      | Diet <sup>3</sup>   |      | Off diet                                    |      | Diet <sup>3</sup>    |      | No diet  |      |                       |      |
| Fasting  | 102               | 1+                | 100     | 0    | 87                   | 0    | 120            | Tr.  | 129   | 0    | 96  | 0    | 118                  | 1+   | 105      | 0    | 109                   | 1+   |
| ½ hour   | 147               | 4+                | 182     | 3+   | 208                  | 2+   | 221            | 4+   | 240   | 1+   | 140   | 0    | 179                  | 3+   | 140      | 2+   | 196                   | 3+   |
| 1 hour   | 86                | 4+                | 189     | 4+   | 217                  | 4+   | 231            | 4+   | 273   | 4+   | 167   | 2+   | 186                  | 4+   | 131      | 4+   | 120                   | 4+   |
| 2 hours  | 59                | 4+                | 107     | 4+   | 106                  | 4+   | 170            | 4+   | 176   | 4+   | 105   | 2+   | 124                  | 4+   | 68       | 4+   | 126                   | 4+   |
| 2½ hours | 51                | 4+                | 55      | 4+   | 50                   | 4+   | 122            | 4+   | 138   | 4+   | 90  | 2+   | 51                   | 4+   | 53       | 2+   | 74                    | 1+   |
|          | Wt. 127 lb.       |                   |         |      | Diminished tolerance |      | Chemical stage |      | Wt. 115 lb.; early clinical stage; month preceding, fatigue, polyuria, nocturia |      | Wt. 122 lb.; recovery; symptoms disappeared |      | Diminished tolerance |      | Recovery |      | Recovery; wt. 126 lb. |      |

Note: Patient was last seen in 1938. No symptoms of diabetes.  
<sup>1</sup> B.S. Blood sugar.  
<sup>2</sup> U.S. Qualitative urinary sugar.  
<sup>3</sup> Diet: C, 225; E, 56; P, 75.

CASE 2

R. B., male, age 19, referred because of glycosuria. No symptoms and negative family history of diabetes. Weight, 98% of normal.

|          | 5/3/38   |      | 2/3/39   |      | 6/9/39                                   |      |
|----------|--|------|--|------|--|------|
|          | B.S.   | U.S. | B.S.   | U.S. | B.S.                                     | U.S. |
|          | No diet  |      | Diet <sup>1</sup>                                    |      |  |      |
| Fasting  | 133  | 0    | 260  | 4+   | 129                                      | 0    |
| ½ hour   | 204  | 0    | 401  | 4+   | 221                                      | 0    |
| 1 hour   | 266  | 4+   | 455  | 4+   | 289                                      | 4+   |
| 2 hours  | 241  | 4+   | 455  | 4+   | 259                                      | 4+   |
| 2½ hours | 212  | 4+   | 398  | 4+   | 212                                      | 4+   |
|          | Wt. 145 lb.; early chemical stage; no symptoms |      | Wt. 142 lb.; clinical stage; polyuria and polydipsia |      | Wt. 136 lb.; chemical stage; no symptoms |      |

Note: This patient was seen last in April, 1940. All fasting blood sugars normal and only an occasional trace of sugar after meals.  
<sup>1</sup> Diet, C, 164; F, 56; P, 60.

CASE 3

A. B., female, age 19; negative family history. Weight, 98% of normal.

|          | 12/23/37       |      | 2/24/38        |      | 11/27/38                       |      |
|----------|----------------|------|----------------|------|--------------------------------|------|
|          | B.S.           | U.S. | B.S.           | U.S. | B.S.                           | U.S. |
|          | No diet        |      | No diet        |      |                                |      |
| Fasting  | 142            | 0    | 147            | 0    | Developed symptoms of diabetes |      |
| ½ hour   | 212            | 0    | 226            | 0    |                                |      |
| 1 hour   | 300            | 3+   | 273            | 3+   |                                |      |
| 2 hours  | 263            | 4+   | 275            | 4+   | Clinical stage                 |      |
| 2½ hours | 253            | 4+   | 248            | 4+   |                                |      |
|          | Chemical stage |      | Chemical stage |      |                                |      |

Note: Patient refused to return in June, 1938, for further study.

CASE 4

D. M., male, age 19; no family history of diabetes. No symptoms. Referred because of transient glycosuria.

|          | 1/17/36     |      | 1/1/37  |      | 12/8/37 |      | 4/15/40                           |      |
|----------|-------------|------|---------|------|---------|------|-----------------------------------|------|
|          | B.S.        | U.S. | B.S.    | U.S. | B.S.    | U.S. | B.S.                              | U.S. |
|          | No diet     |      | No diet |      | No diet |      |                                   |      |
| Fasting  | 75          | 0    | 61      | 0    | 90      | 0    | 130                               | 0    |
| ½ hour   | 106         | Tr.  | 155     | 2+   | 162     | 0    | 149                               | 3+   |
| 1 hour   | 99          |      | 138     | 3+   | 152     | 3+   | 204                               | 4+   |
| 2 hours  | 91          | 2+   | 94      | 4+   | 126     | 2+   | 170                               | 4+   |
| 2½ hours | 68          | Tr.  | 98      | 0    | 131     | 1+   | 147                               | 4+   |
|          | Wt. 169 lb. |      |         |      |         |      | Wt. 171 lb.; early chemical stage |      |

CASE 5

E. H., female, age 28; no family history of diabetes. No symptoms except mild pruritis vulvae.

|          | 6/3/38         |      | 12/20/39       |      |
|----------|----------------|------|----------------|------|
|          | B.S.           | U.S. | B.S.           | U.S. |
|          | No diet        |      |                |      |
| Fasting  | 176            | 4+   | 157            | 0    |
| ½ hour   | 259            | 2+   | 266            | 2+   |
| 1 hour   | 315            | 4+   | 272            | 4+   |
| 2 hours  | 337            | 4+   | 204            | 4+   |
| 2½ hours | 315            | 3+   | 170            | 4+   |
|          | Chemical stage |      | Chemical stage |      |

Note partial recovery of this patient in spite of no treatment.

## CASE 6

R Dab, male, age 24, referred because of loss of weight, fatigue and transient glycosuria

|                    | 6/2/34                            |    | 10/25/34               |    | 2/25/35                |    | 2/4/37                              |    |
|--------------------|-----------------------------------|----|------------------------|----|------------------------|----|-------------------------------------|----|
|                    | BS                                | US | BS                     | US | BS                     | US | BS                                  | US |
|                    | Diet <sup>1</sup>                 |    | No diet                |    | No diet                |    |                                     |    |
| Fasting            | 129                               | 0  | 72                     | 0  | 102                    | 0  | 99                                  | 0  |
| $\frac{1}{2}$ hour | 228                               | 0  | 72                     | 0  | 138                    | 0  | 155                                 | 0  |
| 1 hour             | 267                               | 4+ | 114                    | 0  | 165                    | 0  | 196                                 | 0  |
| 2 hours            | 186                               | 4+ | 147                    | 0  | 98                     | 0  | 128                                 | 0  |
| 2½ hours           | 171                               | 0  | 110                    | 0  | 100                    | 0  | 136                                 | 0  |
|                    | Wt 144 lb<br>early clinical stage |    | Wt 130 lb<br>recovered |    | Wt 145 lb<br>recovered |    | Wt 145 lb<br>7 early chemical stage |    |

<sup>1</sup> Diet, C, 215, F, 60, P, 72

## CASE 7

M H, male, age 38, referred because of persistent glycosuria No symptoms

|                    | 5/8/32   |    | 12/2/32                       |    | 5/16/33           |    | 11/21/33 |    | 6/21/34                                       |    |
|--------------------|--|----|-------------------------------|----|-------------------|----|----------|----|---|----|
|                    | BS   | US | BS                            | US | BS                | US | BS       | US | BS  | US |
|                    | Diet <sup>1</sup>                                |    | Off diet                      |    | Diet <sup>1</sup> |    | Off diet |    |   |    |
| Fasting            | 74   | 0  | 82                            | 0  | 80                | 0  | 95       | 0  | 124   | 0  |
| $\frac{1}{2}$ hour | 105  | 0  | 112                           | 0  | 135               | 0  | 100      | 0  | 195   | 0  |
| 1 hour             | 204  | 4+ | 140                           | 1+ | 165               | 0  | 145      | Tr | 193   | 2+ |
| 2 hours            | 173  | 4+ | 120                           | 0  | 167               | 0  | 135      | 1+ | 217   | Tr |
| 2½ hours           | 157  | 3+ | 105                           | 0  | 135               | 0  | 98       | Tr | 163   | 0  |
|                    | Wt 214 lb<br>no symp<br>toxic<br>chemical stage? |    | Wt 206 lb<br>no symp<br>toxic |    | No symp<br>toxic  |    | Recovery |    | Wt 204 lb<br>polyuria<br>early clinical stage |    |

<sup>1</sup> Diet, C, 275, F, 56, P, 78

## CASE 8

W S, age 50, no family history of diabetes No symptoms except fatigue

|                    | 12/20/39  |    |   | Date     | C   | Diet | P  | BS  | US | Weight, lb |
|--------------------|-----------|----|---|----------|-----|------|----|-----|----|------------|
|                    | BS        | US |   |          |     | F    |    |     |    |            |
| Fasting            | 204       | 0  | Patient given dietary therapy. No postprandial glycosuria after 1/15/40. Diet increased slowly as indicated in columns at right | 12/20/39 | 56  | 56   | 42 | 204 | 0  | 178        |
| $\frac{1}{2}$ hour | 297       | 2+ |   | 1/15/40  | 74  | 56   | 45 | 124 | 0  | 173        |
| 1 hour             | 367       | 3+ |   | 2/7/40   | 92  | 56   | 48 | 124 | 0  | 164        |
| 2 hours            | 330       | 3+ |   | 4/2/40   | 182 | 60   | 63 | 116 | 0  | 162        |
| 2½ hours           | 310       | 4+ |   |          |     |      |    |     |    |            |
|                    | Wt 178 lb |    |   |          |     |      |    |     |    |            |

## CASE 9

M T, male, age 54, negative family history of diabetes and no symptoms

|                    | 4/23/36                   |    | 2/24/37             |    | 8/5/38               |    |
|--------------------|---------------------------|----|---------------------|----|----------------------|----|
|                    | BS                        | US | BS                  | US | BS                   | US |
|                    | Diet <sup>1</sup>         |    | No diet             |    |                      |    |
| Fasting            | 217                       | 2+ | 99                  | 0  | 49                   | 0  |
| $\frac{1}{2}$ hour | 295                       | 4+ | 140                 | 1+ | 107                  | 0  |
| 1 hour             | 327                       | 4+ | 173                 | 0  | 109                  | 0  |
| 2 hours            | 315                       | 4+ | 131                 | Tr | 114                  | 0  |
| 2½ hours           | 277                       | 4+ | 69                  | Tr | 81                   | 0  |
|                    | Chemical stage, wt 185 lb |    | Recovered wt 150 lb |    | Recovered, wt 173 lb |    |

Note. Patient last seen in 1939. Had no symptoms or postprandial glycosuria

<sup>1</sup> Diet, C, 236, F, 56, P, 72

If these patients are properly treated by diet alone it is possible to reverse the metabolic process that is taking place and attain a normal carbohydrate metabolism as indicated by the glucose tolerance test. The fact that this can be accomplished indicates that, in diabetes mellitus, the underlying pathology is not necessarily a lack of insulin, but that there may be a failure of its proper utilization by the body.

## CASE 10

E von B, female, age 50, normal weight. Family history of diabetes. Referred because of failing vision, fatigue, polyuria, polydipsia and neuritis

|                    | 8/22/39           |    | 4/8/40                      |    | 12/31/40    |    |
|--------------------|-------------------|----|-----------------------------|----|-------------|----|
|                    | BS                | US | BS                          | US | BS          | US |
|                    | Diet <sup>1</sup> |    |                             |    |             |    |
| Fasting            | 275               | 2+ | 124                         | 0  | 78          | 0  |
| $\frac{1}{2}$ hour | 362               | 4+ | 196                         | 0  | 97          | 0  |
| 1 hour             | 447               | 4+ | 253                         | 0  | 150         | 0  |
| 2 hours            | 465               | 4+ | 247                         | 2+ | 172         | 1+ |
| 2½ hours           | 440               | 4+ | 226                         | 2+ | 153         | 1+ |
|                    | Clinical stage    |    | Chemical stage, no symptoms |    | No symptoms |    |

Note. This case is presented to show results of treating severe diabetic early in the development of the disease

<sup>1</sup> Diet, C, 150, F, 70, P, 55

The answer as to what will ultimately happen to these treated patients can be known only in future years. An attempt is being made to follow all of these patients in order to determine whether or not they develop clinical diabetes in spite of following instructions in regard to the diet and the maintenance of proper weight.

CASE 11

M. F., female, age 62. Negative family history of diabetes. October, 1940, noted symptoms of nocturia, polyuria, polyphagia and gain of 15 pounds of which she had lost 17 pounds by the time she was seen, giving her a normal weight.

|         | 3/14/41 |    | 4/22/41 |    | Date    | Diet |    |    | Weight, lb | Fasting Blood Sugar |
|---------|---------|----|---------|----|---------|------|----|----|------------|---------------------|
|         | BS      | US | BS      | US |         | C    | F  | P  |            |                     |
| Fasting | 122     | 0  | 92      | 0  | 3/12/41 | 56   | 56 | 42 | 140        | 140                 |
| ½ hour  | 213     | 0  | 166     | 0  | 3/23/41 | 74   | 56 | 45 | 138        | 120                 |
| 1 hour  | 278     | 2+ | 187     | 0  | 3/30/41 | 92   | 56 | 48 | 137½       | 110                 |
| 2 hours | 333     | 3+ | 148     | 0  | 4/ 7/41 | 110  | 56 | 51 | 134        | 130                 |
| 3 hours | 244     | 2+ | 80      | 0  | 4/17/41 | 128  | 60 | 60 | 133½       | 105                 |
|         |         |    |         |    | 8/12/41 | 150  | 70 | 70 | 126        | 80                  |

Note A case of rather dramatic and maintained recovery from clinical diabetes

SUMMARY

Glycosuria is of clinical significance. The development of diabetes in young adults is slow and resolves itself into four stages, respectively: a), diminished tolerance; b), diminished tolerance and assimilation; c), chemical diabetes; d), clinical diabetes.

Excellent results may be accomplished by diet alone, and there may be a return to normal tolerance if therapy is instituted in patients of Groups III and IV, A. In early clinical diabetes results are satisfactory, but if the condition progresses and severe symptoms occur, good results become more difficult to attain.

In this age group the presence of obesity or a family history of diabetes was not significant in enabling one to predict which of two individuals with disturbed glucose tolerance would ultimately develop diabetes.

Loss of weight alone is not responsible for improvement in tolerance.

The renal threshold for glucose is not stationary. It would appear that after recovery the individual must continue to restrict his diet and maintain a normal or subnormal weight to be able to retain a normal carbohydrate metabolism. Diabetes may not be wholly due to a lack of insulin but rather to a failure in utilization of insulin by the body.

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2. WATSON, B. A.: *Minnesota Med.* 16: 566. 1933.  
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CASE 12

H. C., male, age 19. Family history of diabetes, weakness, polyuria, polyphagia, polydipsia, and glycosuria 4 months preceding first glucose tolerance test.

|          | 10/9/31                        |      | 5/6/32                         |      | 1/1/33                         |      |
|----------|--------------------------------|------|--------------------------------|------|--------------------------------|------|
|          | B.S.                           | U.S. | B.S.                           | U.S. | B.S.                           | U.S. |
|          | Diet <sup>1</sup>              |      | Off diet                       |      |                                |      |
| Fasting  | 113                            |      | 122                            | 0    | 238                            | 4+   |
| ½ hour   | 217                            |      | 176                            | 2+   | 315                            | 4+   |
| 1 hour   |                                |      | 231                            | 4+   | 415                            | 4+   |
| 2 hours  | 388                            |      | 208                            | 4+   | 455                            | 4+   |
| 2½ hours | 340                            |      | 136                            | 4+   | 425                            | 4+   |
|          | Wt. 150 lb.; clinical diabetes |      | Wt. 142 lb., chemical diabetes |      | Wt. 144 lb., clinical diabetes |      |

Note: This patient's second glucose tolerance curve indicates almost complete recovery in that the fasting and two and one-half-hour blood sugars nearly approximate each other.

<sup>1</sup> Diet, C, 275, F, 56; P, 78.



## COMMUNICATIONS TO THE EDITORS

### Influence of Testosterone Propionate on the Size of Uterine Fibroids in Human Male

IN A PREVIOUS communication<sup>1</sup> we were able to demonstrate that small pellets of estradiol benzoate implanted locally into the uterus of guinea pigs produce fibromyomatous tumors in 75 per cent of the animals used. It appeared that androgen implanted simultaneously has a tendency to limit the extent to which the estrogen is able to produce these tumors. In order to determine whether androgen had comparable depressing effects on fibromyomatous tumors in the human female we decided to treat patients having fibroids with testosterone propionate.

This effect has been reported by various workers in the treatment of metrorrhagia in patients in whom fibroid tumors were found to be present. Opinion varies as to the efficacy of this mode of treatment and there are few observations concerning changes in the size of these tumors.

In view of the fact that we will not be able to continue this work further, I would like to report 3 cases in whom testosterone propionate was employed and in whom we were particularly concerned with changes in the size of the uterine fibroids.

Each patient was examined by the writer before, during and after treatment, and by at least one other observer.

**Patient 1, Mrs E M**, a 50-year-old white woman. This patient had a firm uterus the size of a 4 month pregnancy with a subserous tumor on the left side the size of a lemon. This mass on the left side was extremely tender to palpation. She was given 10 mg of testosterone propionate 3 times a week for 20 injections, followed by 3 injections of 25 mg. The menses, which had been regular, continued to be regular although the menstrual flow was somewhat diminished. After 4 injections the pain in the left lower quadrant disappeared, after 17 she was examined and the uterus was found to be smaller, the nodule on the left being about the size of a walnut and much less tender. One month after treatment had been stopped, pelvic examination revealed the uterus as slightly larger than normal with only a suggestion of a tumor on the left side. Four months later, 5 months after treatment had been stopped, both the uterus and the fibroid on the left side were found to be larger although not as large as when treatment was originally begun.

**Patient 2, Mrs I P**, a 44 year-old white woman whose chief complaint was profuse menstrual flow, was found to have fibroids the size of a 3-month pregnancy. She was given 25 mg of testosterone propionate twice a week for 37 injections. The menses, which had been regular, remained regular with the exception of one month when she did not have a menstrual period, this was early in the course of treatment. The flow became quite normal. At the end of this course of treatment the uterus was found to be slightly larger than normal with a fibroid prominence on the anterior surface. At this time the patient complained of some deepening and hoarseness of the voice, and mild facial acne. One month later the acne had improved and the hoarseness had disappeared. Two months later, 3 months after cessation of treatment, the uterus had regained its original size which has been maintained to date. The menstrual periods have been normal and regular 8 months after cessation of treatment.

**Patient 3, Miss N B**, a 29-year-old white woman. This patient was found to have several fibroid masses so that the uterus was the size of a 4 month pregnancy with one large fibroid mass on the left side the size of an orange and extending to the umbilicus. She was given testosterone propionate therapy consisting of 20 injections of 25 mg each, twice weekly. At the end of this period of treatment the uterus had become smaller, about the size of a 2- to 3-months pregnancy, and the tumor on the left side, was no larger than a lemon. The menses had been irregular, previously, and were similarly irregular during treatment. The patient complained of some deepening of the voice and increase in facial hirsuties.

**Discussion.** It appears that testosterone propionate may cause a regression in the size of uterine fibroids as well as relieve many of the symptoms produced by these tumors. This effect, however, seems to be temporary, since regrowth occurred in 2 of these patients in whom there was sufficient time to observe the phenomenon.

It would seem that the use of this method of treatment would be limited. Nevertheless, it might prove to be of some value in cases in which it is desirable that the menstrual flow be maintained and in instances in which surgery or x ray are contra indicated.

W. H. PERLOFF

Received for publication May 11, 1942

<sup>1</sup>PERLOFF, W. H., AND R. KURZKOP. Production of uterine tumors in the guinea pig by local implantation of estrogen pellets. *Proc Soc Exper Biol & Med* 46: 262, 1941.

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# CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. Collaborators: E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN DONALDSON, MURRAY B. GORDON, E. C. HAMBLIN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

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## THYROID

GODTFREDSEN, E.

Scotopic vision and liver function under thyrotoxicosis. *Acta med. Scandinav.* 108: 261. 1941.

The author investigated the complex interrelations between thyroid function, liver function, serum cholesterol, and vitamin A metabolism. In 10 cases of thyrotoxicosis he found no significant injury to liver nor marked reduction of serum cholesterol. There was however definite reduction in dark adaptation which was not amenable to administration of vitamin A, but which responded to reduction of the thyrotoxicosis, suggesting that there may be a downward regulation of the vitamin A utilization in the organism due to thyrotoxic injury.—F. R. Vanzant (courtesy *Biol. Abstracts*).

JOHNSTON, J. A.

Factors influencing retention of nitrogen and calcium in period of growth. V. Further evidence of the anabolic effect of thyroid on calcium metabolism. *Am. J. Dis. Child.* 62: 1172. 1941.

Continuous determinations of Ca and N balance with concurrent determinations of B.M.R. for the entire time were carried out on 2 girls, who were given desiccated thyroid substance. With a constant intake of food, prolonged bed rest, small doses of thyroid resulted in increased retention of Ca and larger doses produced a decreased retention. The amount of thyroid resulting in a maximal utilization of Ca reduced N retention. Total retention of both was increased by an increased intake of food, which was refused when the metabolism was low and taken well when the metabolism was elevated by thyroid.—M.B.G.

KEARNS, J. E., JR., AND P. STARR.

So-called "iodine resistant" hyperthyroidism. *J. Gynec. & Obst.* 74: 256. 1942.

A satisfactory method is described for the care of perthyroid patients in whom the initial effect of I was sufficient to insure safe operation and in whom the consequent delay resulted in a rising basal rate with aggravation of symptoms. In these people gradual reduction in amounts of I given to the point of an I-free diet was practiced. This I-free regime was persisted in for 2 to 4 months with careful observation. Thereafter the patients could be satisfactorily prepared for surgery in the usual way.—A.T.K.

KOWALLIS, G. F., S. F. HAINES AND J. DE J. PEMBERTON

Goiter with associated myasthenia gravis. Report of 3 cases of exophthalmic goiter and 1 case of adenomatous goiter with hyperthyroidism. *Arch. Int. Med.* 69: 41. 1942.

Exophthalmic goiter with associated myasthenia is common, but exophthalmic goiter accompanied by myasthenia gravis of the bulbar type is rare. Three cases of exophthalmic goiter combined with myasthenia gravis of the bulbar type and 1 case of adenomatous goiter with hyperthyroidism and myasthenia gravis are presented in this excellent contribution. In 1 of these cases subtotal thyroidectomy has been performed successfully, with relief of symptoms of both conditions. Surgical treatment of exophthalmic goiter complicated by myasthenia gravis offers certain difficulties. It is important that the patient be able to cough and to swallow in order to dispose of tracheal mucus, which often appears after thyroidectomy. In the instance herein recorded in which thyroidectomy was performed, treatment with prostigmine resulted in satisfactory improvement in muscular strength.—I.B.



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## Control of Blood Sugar

[A Review Article]

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THE MAINTENANCE of a constant blood-sugar level of around 100 mg. is one of the most important functions of those organs concerned with the proper fuel regulation of the body. These include, besides the obvious 'supply' organs (sensory, central nervous system and digestive tract), most of the organs of internal secretion, and the liver. The co operative working and interplay of all these tissues to keep the blood sugar at a proper level is one of the most illuminating examples of the constancy of the internal environment of Claude Bernard or homeostasis of Cannon.

There are 3 main factors in this regulation besides the obvious absorption of sugar from the intestinal tract. They are a), the rate of oxidation of glucose by the tissues, b), the production of dextrose from other substances by the liver, and c), the storage of glucose as glycogen, fat, and other derivatives.

The liver has much to do with the adjustments and interrelations of these factors. The organ is to the blood sugar what the heart is to the circulation. The blood-sugar level cannot be maintained without it and most of the other organs that aid in the work, do so by acting through it. The liver, through its functions of storage and release of glycogen, conversion of other substances to glucose, and conversion of glucose to fat, effects the proper adjustments in the blood sugar. When the supply of carbohydrate from

the gastro intestinal tract exceeds the utilization rate of the tissues, the liver largely absorbs the excess and converts it to glycogen and fat. Contrariwise, when the food supply is less than the tissue needs, the liver sets free glycogen and starts converting protein to glucose.

### Glucose Needs of Tissues

One of the important endeavors of workers in the field of intermediary metabolism has been the measurement of the rate of glucose utilization, of the tissues of the body. For this purpose one should study the animal in the post-absorptive state in order to eliminate the variables of intestinal absorption and storage of glucose. With these activities eliminated, we have a condition in which the supply of glucose to the blood by the liver closely balances the utilization of it by the tissues.

A requirement for any method purporting to measure this glucose uptake by the tissues is that the animal be maintained in conditions as close to normal as possible. Three methods satisfying this most closely are: a), measurement of the glucose requirement of the body after liver removal; b), measurement of the sugar output by the liver of the intact animal, c), measurement of the glucose utilization of specific tissues or regions of the body in the intact animal. Other methods such as perfusion and tissue slice metabolism determinations entail having the living agent in such unnatural conditions that it would be

extremely hazardous to draw conclusions from observations based on them. Tissue culture measurements have interesting possibilities but great caution must be used in drawing conclusions from them.

*Measurements in hepatectomized animals.* For a period of some hours after surgical removal of the liver from the fasting animal it maintains the normal physiological activity of all other tissues insofar as we can quantify them (1). With the sole source of glucose removed, the sugar in the blood will steadily drop as the tissues use it up. The utilization rate can then be measured by determining the rate at which glucose must be injected to maintain it at a constant level in the blood. Mann (2) reports that this rate is 250 mg. per kg. per hour in the dog; it is 125 mg. per kg. per hour in the rabbit (3). Russell (4) reports the utilization by the eviscerated rat as 135 mg. per kg. per hour.

*Output of sugar by the liver.* Undoubtedly the method of choice for measuring the glucose utilization of the body would be the determination of the output of this substance by the liver in the intact animal. The concentration of sugar in the blood entering and leaving the liver can be accurately estimated. In actual practice, however, this method has many pitfalls. It is extremely difficult to obtain true blood samples without disturbing the circulation of this organ. Furthermore the blood flow through the organ must be very variable, or the estimation of it must be precarious, in order to give the wide range of figures that have been reported for its value (5-10). Since workers who have measured blood-sugar differences between blood entering and leaving this organ have used average figures for blood flow of other observers their results contain the error<sup>1</sup> inherent in taking the product of the averages of two series.

Wierzuchowski and Fiszal (11), on anesthetized operated dogs that had been fasted 28 hours, found an increase of 15.6 mg. of glucose per 100 cc. of blood in its passage through the liver. They estimate this as indicating that the liver supplies the tissues 228 mg. of glucose per kg. per hour. Heller (12) found an increase of 17.2 mg. per 100 cc. of blood going through the liver which he calculates as equivalent

to a new production of glucose of 240 mg. per kg. of body weight per hour. The blood sugar and blood lactic-acid levels of his animals are surprisingly high for fasted phlorizinized animals and would indicate a considerable divergence from normal conditions caused by the operative procedures and anesthetic. Cherry and Crandall (13) made use of the London cannula technique in unanesthetized dogs and, judging from their description and the blood sugar and lactic acid levels, the conditions in their experiments must have been about as close to natural as is possible. They did not measure blood flow through the liver but using the average figure of Blalock and Mason (14), they calculated that the liver supplies sugar to the blood at the rate of 150 mg. per kg per hour in dogs fasted 18 hours. Recently, Crandall and Lipscomb (15) have developed a method for simultaneous determination of blood flow and blood-sugar difference for the liver. They determine the blood flow by determining the urea difference in the blood entering and leaving the liver and dividing this difference into the amount of urea excreted in the urine in unit time. They report that the glucose production never exceeds a rate of 160 mg. per kg. per hour.

*Measurement of individual tissue utilization.* The determination of the drop in blood sugar on passing through the other tissues of the body can also give valuable information concerning glucose utilization. It should be carried out on the intact unanesthetized animal and great care must be observed in the taking of the blood samples lest effects be produced on the blood flow or the tissue metabolism. The blood-sugar difference should be corrected for lactic-acid increase. The determination of the glucose utilization of the whole body with this method would be tedious, requiring arterio-venous blood-sugar differences and the blood flow determinations for all regions of the body.

In dogs fasted 18 hours Cherry and Crandall (13) found the arterio-venous blood-sugar difference for the legs to be 4.8 mg. per cent and for the intestines 2.9 mg. per cent. The simultaneous increases in blood lactic acid were 3.1 and 0.68 mg. per cent, respectively. For the leg of the 18-hour fasted dog Cori, Fisher, and Cori (16) report an average of 2.2 mg. per cent blood-sugar decrease for 13 determinations, and an increase of 1 mg. per cent of blood lactic acid in 2 determinations. Earlier work does not differ essentially from that reported by these two groups, and is reviewed by them. Wierzuchowski and Fiszal (11) determined the arterio-venous blood sugar and blood-lactic acid differences on 11 dogs fasted 8 hours. The average decreases in sugar of blood passing through muscle, head, and intestines were 4.6, 10.3, and 1.9 mg. per cent, respectively, and of these, blood lactic acid increases accounted for 56, 14, and 164 per cent, respectively.

<sup>1</sup> This error may be illustrated with the following simplified case.

Suppose the output of sugar by a given liver is constant but the blood flow through it is variable.

|               | Bloodflow<br>per minute | A-V<br>difference | Output of sugar<br>per minute |
|---------------|-------------------------|-------------------|-------------------------------|
| Condition (1) | 100 cc.                 | 1 mg.             | 100 mg.                       |
| Condition (2) | 10 cc.                  | 10 mg.            | 100 mg.                       |
| Averages      | 55 cc.                  | 5.5 mg.           | 302.5 mg.                     |

The interesting feature of this error is that its always gives values higher than the actual values. There can be no hope of minus and plus errors cancelling each other.

### *Effect of Fasting on Sugar Utilization of Tissues*

Hofmeister (17) many years ago reported that the fasting organism is more susceptible to alimentary glycosuria than the well fed one. This condition, which has been described by many others since, is known as 'starvation diabetes'. This might suggest that the tissues of the fasting animal use less sugar than those of the fed, but not necessarily so. The blood sugar curve after feeding sugar does not give us any information about tissue utilization prior to the feeding. It would give some indication of this for the period after feeding but this will depend on mechanisms such as hormones, put into action as a result of the feeding. To determine this we must keep the blood sugar at its normal level and avoid the action of the liver in storing sugar or in making new sugar. This means using one of the special techniques mentioned previously.

Bergman and Drury (18) have shown that a pre-operative fast diminishes the sugar requirement of the eviscerated rabbit from 206 mg per kg per hour for fed animals to 110 mg per kg per hour for those fasted 4 days. No corresponding study of dogs has been made, but Mirsky (19) reports 140 mg per kg per hour maintains the blood sugar of the 4 day fasted dog after evisceration, which is lower than the figures given by other workers for unfasted dogs. Drury, Bergman, and Greeley (20) found that 80 mg per kg per hour maintains the blood sugar of the hepatectomized dog that has been fasted and phlorizinized for 4 days before operation. Crandall et al (21) using the London cannula technique, have found that fasting for more than 3 days reduces the amount of glucose liberated by the liver into the hepatic vein almost 50 per cent.

These results are in keeping with the findings with tissue and urine analyses during the first day of the fast. During this period the liver glycogen drops rapidly indicating a considerable supply of glucose from this source. In the dog it would appear that glycogen continues to be given up in considerable quantities in the second and even third days. Assuming the liver as 2.7 per cent of the body weight and containing 10 per cent glycogen at the start of the fast this could readily supply 100 mg of glucose per kg per hour for 24 hours and still have an appreciable amount of glycogen left. Benedict (22) estimates 65 and 25 gm of glycogen, respectively, metabolized during the first and second days of fasting in man.

Not only is there evidence of a supply of glucose from glycogen during the first day or two of a fast, but there would seem to be more protein metabolized per hour as compared with later days of fasting. The evidence for this is summarized by Lusk (23) and

shows this extra protein metabolized in the first days of a fast may give rise to as much glucose as that coming from glycogen. There is, then, during the first two or three days of fasting, utilization of both liver glycogen and protein. Later in the fast, protein becomes the only source of glucose and this utilization is diminished in amount.

The evidence from these divergent sources indicates that the tissues of the dog are supplied with between 200 and 300 mg of sugar per kg per hour during the first day of fast and that by the fourth day it has been diminished to between 50 and 100 mg per kg per hour. The time required to bring about this change does not necessarily obtain for other species, by and large the smaller the animal, the more rapid the change. We might reasonably expect the mouse to show as much change in 24 hours as does the dog in 4 days.

This indicates that during extended fasting, but a small fraction of the total fuel requirement of the tissues is supplied by glucose, perhaps not more than 10 per cent. In view of the fact that the fuel of the central nervous system seems to be almost entirely glucose (24), one might well ask if the requirement of this tissue does not account for all of this substance used by the fasting organism. Mulder and Crandall (25) find the arterio-venous difference for the brain to be just as great (10 mg of sugar per 100 cc of blood) for the 6 day fasted dog as that of the recently fed animal. In the present state of our knowledge of metabolism it would be best to recognize two types of glucose utilization by tissues, one peculiar to the brain and the other shared by all other tissues. The rate of the former is high and practically constant under all conditions. The rate of the latter varies greatly according to circumstances. It is high in normal, fed animals, and is low in fasting ones.

### *Production of Glucose from Other Substances by the Liver*

*Conversion of protein to glucose.* The work of Bollman and Mann (26) definitely shows that this transformation is carried out only by the liver. Much work has been done attempting to determine how much glucose can be obtained from a given amount of protein. Earlier workers believed that the amount of glucose obtainable was 40 to 60 per cent of the weight of protein transformed. These values were based on results obtained in depancreatized and in phlorizinized dogs. When these animals were fed protein, extra sugar was excreted in the urine in an amount representing 40 to 60 per cent of the fed protein. The assumption was made that the tissues of these animals used no glucose. In the light of recent work which shows that at least one important tissue, the central nervous system, uses glucose almost ex-

clusively at all times and under all conditions' (24), this assumption can no longer be maintained. Drury Bergman, and Greeley (20) have measured this glucose utilization by the tissues of the phlorizinized dog. When this amount is added to that excreted in urine, a total is obtained which would necessitate the conversion to sugar of 80 to 90 per cent of the catabolized protein in order to supply this. Results in protein feeding experiments with depancreatized dogs confirm this conversion figure (27).

At the beginning of a fast the glucose needs of the body come from stored glycogen and protein which is converted by the liver. The glycogen stores in small animals such as the rat are largely exhausted in a day or two; they last as long as 3 or 4 days in larger animals such as the dog and man. However, as the fast continues the body depends more and more on protein for its sugar. After 4 days of fasting this is probably the sole source. During the first 2 days of a fast this protein comes largely from that stored by the liver itself. After this the other tissues yield relatively more protein (28). After the third and fourth day of fasting the glucose needs of the body are supplied almost entirely by the liver from conversion of protein from the general body tissues.

Little is known concerning the mechanism controlling the breakdown of body protein under physiological conditions. Under ordinary circumstances the controlling mechanisms adjust this breakdown nicely to the glucose utilization of the tissues so that we do not get large imbalances with corresponding fluctuations in blood sugar. Recent work (29) has shown that it is not exactly correct to speak of body protein breakdown and of body protein regeneration as two distinct and mutually exclusive processes. These two processes are going on simultaneously at all times, it is the balance between them that shifts. Thus when the body is in 'negative nitrogen balance' the process of body protein breakdown is greater than that of regeneration. The processes of breakdown and regeneration of body proteins are not simply the reverse of each other, physiologically speaking. Body protein breakdown means setting free amino acids which go to the liver to be changed to glucose together with urea which is excreted. Body protein can give rise to glucose in this way, but we cannot make body protein by feeding glucose, although we can diminish the breakdown during fasting by giving glucose. The liver is an important factor in this control of breakdown and building of body protein. It converts the amino acids from the breakdown to a ready fuel, glucose, and when the body is building up protein it must allow the amino acids of the food to pass through it and not change them to glucose. In severe diabetes we have a state in which the liver is not properly controlled in this respect; the liver converts to glu-

cose any exogenous protein which thereby is useless to the tissues for building up purposes even though they may be greatly exhausted in protein material. The mechanism of the control of this activity of the liver remains one of the most important problems of protein metabolism yet to be worked out.

The mechanism of the control of body protein breakdown is also a problem needing investigation. It seems to be closely related to the glucose utilization of the tissues. When the latter is high, e.g. after carbohydrate feeding or insulin administration, the rate of body protein breakdown is very low. When it becomes low, as in fasting, there is an increase in body protein breakdown. In untreated diabetes there seems to be a low rate of tissue utilization of glucose during fasting and a high body protein breakdown is to be expected. One can simplify our ideas about body protein breakdown and carbohydrate metabolism if one takes the concept as a working hypothesis that any condition which decreases glucose utilization by the tissues increases body protein breakdown. Conversely, when we have a condition in which glucose utilization is low and body protein catabolism is high, we will find that this latter will be decreased by any mechanism which increases the former. By utilization one does not necessarily understand oxidation of glucose since transformation to intermediate forms may serve as well.<sup>2</sup> At the present time very little is known about the immediate fate of glucose which disappears from the body fluids. A clear distinction must be kept between blood-sugar level and glucose utilization rate. As will be illustrated later in the paper, the blood-sugar level may be high with a simultaneously low utilization rate, or vice versa. This point will be reviewed later after having taken up special cases illustrating it.

*Conversion of other substances to glucose.* The liver can convert many other substances such as lactic acid, pyruvic acid, and other monosaccharides into glucose. The possibility of conversion of fat to sugar by the liver is always a very tempting idea. In taking recourse to it the theorist saves himself a great deal of bother with exact study of nitrogen and glucose balances. However, this concept has not been the theory of those who have insisted on rigid observance of extreme care in experimental procedures and care-

<sup>2</sup> By utilization is meant the change of glucose to some other chemical state which can be disposed of, or deposited in a form in which it can remain indefinitely without prejudice to the body's normal functioning. Complete oxidation is such a process since the chemical products,  $\text{CO}_2$  and  $\text{H}_2\text{O}$  can be readily disposed of. Conversions to glycogen and fat are also such processes since the products can be deposited and stored without interference to the normal economy of the body. Conversion to lactic acid or pyruvic acid could not be so classified since these substances cannot be deposited or readily excreted. Rather, they accumulate in the blood and body fluids and will, and if this is persisted in, interfere with the normal physiological operation of the body

ful analysis of results. In the past, many claims of a demonstration have been made but all have fallen down on subsequent checking of the experiments. However, at the present time, we cannot claim the impossibility of conversion of fat to sugar. It is possible that some day a definite demonstration of this transformation may be forthcoming. Until such time it is better to discard the idea not only because it has not been proven, but because it is unnecessary. The facts of metabolism and diabetes can be more simply explained and understood without this complicating hypothesis. Besides this, there are some suggestive facts which point against it. Thus, the feeding of fat to the diabetic or phlorizinized animal does not lead to an increased excretion of sugar as does protein feeding. This, its proponents say, is because the liver is already handling all the fat it can. However, there is evidence of the liver doing something to the extra fat, for an increased ketone body production occurs. Furthermore, such a liver will produce sugar if supplied with fatty acids containing an odd number of carbon atoms (30).

*Conversion of glucose to storage products by the liver.* The capacity of the liver to store glucose in the form of glycogen is well known. This organ can store glycogen up to a concentration of 10 per cent. This accounts for more glucose than it might seem at first glance, since the weight of the liver will be as much as doubled when it lays down such large amounts of glycogen. Water seems to account for most of this extra weight. The liver is ordinarily considered as an important factor for the conversion of glucose to fat. However, it has been shown recently that under certain conditions rats with the abdominal viscera removed can have a respiratory quotient above 1.1 when they are given glucose (31). This work indicates that both the liver and peripheral tissues can be sites of fat formation from carbohydrate. This process will be taken up later in the sections on the different endocrines.

#### GLANDS OF INTERNAL SECRETION

The three important factors affecting the blood sugar, a), tissue utilization, b) storage, and c), new formation of glucose are regulated in a remarkably efficient manner since ordinarily little change in blood sugar level occurs despite huge variations in carbohydrate intake and metabolic expenditure. There is no evidence that the peripheral tissues can of themselves vary their glucose consumption to the desired rate needed for the varying conditions of nutrition and metabolism. Thus, any given cell in the periphery does not know that the animal is eating a), a high carbohydrate diet at one time and hence should increase the proportion of glucose in its fuel, or b), know that the animal is fasting and hence should

lower glucose utilization and increase that of fat. The concentration of glucose in the blood may have some small direct effect on the rate of utilization by the body cells (32). The changes in concentration needed to produce such effects are quite outside the physiological range in which the normal body manages to keep, despite large fluctuations in intake and fuel expenditure. This regulation of the type of fuel mixture that the tissues use seems to be effected by the endocrine system. The endocrines also regulate the rate of conversion of glucose to storage products. Their rôle in the new formation of glucose from body protein is uncertain.

The methods of study of these organs are common to all of them. One procedure involves surgical removal of the organ followed by study of the resulting changes in metabolism. The other method consists of studying the changes in metabolism resulting from administration of the active principles of the organs in normal subjects or into those previously deprived of the organ in question. Nature, by disease, sometimes produces the experimental conditions in man which the experimentalist produces in animals by the aforementioned methods.

#### Adrenalin

The immediate rise in blood sugar produced by adrenalin is the result of breakdown of liver glycogen to form glucose. This hormone also causes muscle glycogen to break down to lactic acid. The latter is carried by the blood stream to the liver where it is changed to glucose or glycogen. Adrenalin, then, will cause a primary drop in liver glycogen followed by a rise, which in some species, may carry it to higher levels than those of control animals. Adrenalin seems to be an agent which liberates stored sugar (glycogen) into the blood for extra needs in emergency conditions.

#### Thyroxin

Thyroxin does not seem to have any immediate effect on carbohydrate metabolism. Continued administration of this hormone results in depletion of glycogen stores. At this stage the animal may become hypoglycemic, be hypersensitive to insulin, and show relatively little response to adrenalin. The changes do not necessarily indicate any specific action of thyroxin on carbohydrate metabolism. These changes may mean merely carbohydrate depletion resulting from the generally increased metabolic rate. As a result of the latter, all stored foodstuffs will tend to be depleted.

#### Insulin

*Mode of action of insulin.* The action of insulin at the present time cannot be completely explained as one process, there are at least three actions related to

carbohydrate metabolism which may be produced under different conditions.<sup>4</sup> Whether these three are all resultants of one fundamental underlying process cannot be answered at this time and with our present knowledge of metabolism. These three actions are: a). Inhibition of excessive breakdown of body protein to form sugar. b). Increase in storage or disposal of fed carbohydrate; that is, assimilated carbohydrate that is not needed for immediate current needs but which is put away for fuel needs at a later time. The known forms in which this can be disposed of are muscle and liver glycogen, and body and liver fat. c). Increase in immediate oxidation of glucose.

These effects have been demonstrated in the depancreatized dog and cat. These diabetic animals when not given insulin, exhibit a) excessive breakdown of body protein, b) an inability to store fed carbohydrate and c). some impairment in capacity to oxidize glucose. Administration of insulin to such animals corrects these deficiencies and so brings about the actions listed above.

It is only in recent years that the effects of pancreatectomy in such animals as the goat, monkey, and rabbit have been studied (33-37). The resulting diabetes is much milder than in the pancreatectomized dog and cat, so that the animals can survive without insulin administration. The animals can maintain their weight and keep in nitrogen balance without severe ketosis on a high carbohydrate diet. Insulin seems necessary to produce an increase in weight on such a regime (38). The results in these animals show that insulin is not a necessity for the oxidation of glucose. Furthermore, the capacity of the tissues of these animals to utilize appreciably large amounts of carbohydrate is probably the reason they can be maintained in nitrogen balance; there is not the stimulus to tissue protein catabolism which, in the depancreatized dog, is the low rate of glucose utilization of the tissues. The results in these animals should be given more attention in forming our ideas of insulin action. Our notions in this connection have become too fixed by findings in the depancreatized dog. That this animal was the first to be depancreatized and was the only preparation studied during the early years of investigation in this field, is no reason for its tyrannizing our thinking in this regard. The depancreatized goat and monkey, although studied more recently, should have just as much weight in our consideration and conclusions. The depancreatized rat can be maintained in good condition on a high

carbohydrate diet without insulin. He can keep nitrogen balance, ketosis is not present and he util a considerable amount of sugar. On such a diet cannot gain weight without insulin, and any weight lost during a fast cannot be regained by subsequent feeding except with the aid of insulin (38). On a diet containing appreciable amounts of fat he will run up weight.

Recently Tepperman et al. (31) have found that rats can be trained to eat their daily food in 3 hours. When such rats are eviscerated and given insulin excess glucose they show respiratory quotients of 1.0 or over, indicating that the peripheral tissues of the trained animals can convert glucose to fat. Untrained control rats show respiratory quotients of less than 1.0 when similarly treated. These results suggest that some long-acting hormone cooperates with the insulin to make possible the conversion by the peripheral tissues of the trained rats. Since, in the untrained rats, fat synthesis can occur it would seem that the liver is the important site for the conversion of glucose to fat and when this organ is removed this process is largely stopped even when insulin and glucose are given.

It is generally assumed that insulin increases immediate oxidation of glucose although the process is not as simple as was once thought. White first believed that insulin had this action because at that time the prevailing theory maintained that the trouble in diabetes was due to an inability to utilize glucose. Since the use of insulin was successful in the treatment of this disease, it was assumed it must increase the oxidation of this sugar. More recent work has furnished good evidence that the depancreatized animal can oxidize glucose in not inconsiderable amounts. This follows from the observation that when the liver is removed from the depancreatized animal, the blood sugar falls and glucose is given in order to keep the animal from going into hypoglycemia. Yater et al. (39) found that the amount of glucose injection necessary to maintain a normal blood-sugar level in a depancreatized-hepatectomized dog was 160 mg. per kg. per hour in contrast to a rate of 250 mg. per kg. per hour needed for the intact tectomized dog. Greeley and Drury (40) find that the diabetic rabbits after evisceration need as much glucose as normal fasted rabbits after hepatectomy. The glucose needed for the diabetic dog may be less than that needed for the brain, and the results may indicate some impairment of utilization by other tissues of the rabbit and other herbivora utilization by the brain and the other tissues of the diabetic animal is probably normal for basal conditions, but is less than normal in the fed condition. The impairment of glucose utilization in the diabetic is, then, not absolute, but varies with the tissue, the species, and

<sup>4</sup> These are the important general effects of insulin ordinarily considered in clinical and metabolic work. Other specific actions have been reported such as increase in pyruvic acid formation (40) and increase in phosphorylation of glucose (51). These would seem to be related to carbohydrate metabolism and may be intermediate steps or reactions secondary to the general effects stated above.

physiological state of the animal. Insulin certainly increases this utilization but to what extent by increasing storage of glucose and to what extent by increasing immediate oxidation is not easy to determine. Some workers have attempted to measure the extent of this latter action by determining the rise in R Q after insulin. However, although a rise in R Q might be due to an increase in immediate oxidation of sugar, it could as readily result from an intermediary change of glucose to some other compound containing less oxygen.

The chief effect of removal of the pancreas, then, is a resultant diminution in utilization of glucose by the animal, particularly for storage. There are significant quantitative differences in the various species but these differences apply only to tissues other than the brain. The utilization of glucose by the brain remains high in all species after pancreatectomy and accounts for a definite portion of the glucose requirement of all depancreatized animals after hepatectomy. The utilization of the other tissues in diabetics varies with the species. In the rat the utilization is sufficient for current needs but is not adequate for storage.

Can it be that insulin has but one pharmacodynamic action and its apparent multiple effects are the results of this fundamental action reacting on different physiological mechanisms? Insulin accelerates the disappearance of glucose in the body. The glucose might well pass through some first chemical stage which could be a bottleneck for the different routes which carry glucose to its different fates, oxidation, or storage as fat, or glycogen. The concentration of the compound representing this first chemical stage might affect secondarily the rate of protein catabolism by the tissues in general. Insulin is not absolutely necessary for the maintenance of nitrogen balance. Most depancreatized herbivora stay in nitrogen balance when fed without insulin. More than a normal amount of body protein is not broken down when they are fasted.

#### Pituitary

Hypophysectomized animals can survive the operation for long periods and in good condition, provided they are fed adequate amounts of carbohydrate or protein. They show a marked drop in blood sugar on fasting, which, in the rabbit usually leads to a fatal outcome in a few hours (41). The fasting hypoglycemia is serious in the rat and often so in the dog. The blood sugar of the hypophysectomized rabbit can be kept at normal levels by constant injection of glucose, Greeley (41) has found that these animals need almost 600 mg per kg per hour to prevent hypoglycemia. In the same way, Russell (4), determined the sugar need of eviscerated rats and eviscerated hypophysectomized rats. For the former, the rate

is 135 mg per kg per hour and for the latter 250 mg per kg per hour.

The hypoglycemia of the fasting hypophysectomized animal has been explained by many authors (42) on the supposition that these preparations are greatly restricted in their capacity to break down body protein for the formation of new glucose. Such a hypothesis cannot account for the differences observed by Russell as noted above, since all of these animals were eviscerated and hence in all, new formation of glucose would be stopped. Even less is this idea capable of accounting for the findings in the rabbit. The normal fasting rabbit breaks down body nitrogen at the rate of 20 mg per kg per hour. This would give rise to about 120 mg of glucose per kg per hour and this is enough to balance the sugar needs of the normal animal. Therefore, even if all protein catabolism were stopped in the hypophysectomized rabbit (as after hepatectomy) the sugar need would increase only to this figure. Actually it is close to five times this amount after hypophysectomy.

The hypophysectomized dog metabolizes protein of the food to the same extent as the normal one. Fasting reduces its nitrogen excretion about 25 per cent below that of the normal. This indicates a reduction in breakdown of tissue protein. However, the percentage reduction of this metabolic process is just about the same as that for the general reduction in basal metabolism. When both types of animal are given phloridzin, in addition to fasting, the difference in nitrogen excretion becomes much greater. The difference in all metabolic processes is probably greatly increased since the blood sugar of the hypophysectomized animals sinks to very low levels under these conditions and they would probably have low body temperatures. Many of them are morbid and some die. The lower nitrogen excretion is probably only partly due to this general slowing up in the metabolic processes. If the rate of utilization of glucose by the tissues is increased by the hypophysectomy there would not be the stimulation for increased body protein breakdown. Some of the results of Houssay and Blassotti (42) show this increase in sugar utilization by the dogs deprived of the pituitary. Table 1 shows the effect of fasting and phloridzin on

<sup>4</sup> At first sight the results of Lee and Ayres (52) might appear to contradict this view. They fed normal and hypophysectomized rats exactly the same amount of food over a period of 30 days. At the end of this time it was found that the hypophysectomized rats had lost more body protein and less body fat than the controls. This may indicate an increased body protein breakdown. However, it could result from a reduced regeneration rate which would be secondary to an increased conversion of food protein to sugar by the liver. In other words, the liver might convert practically all food protein into glucose and the sugar of the animal eating plant would be in negative nitrogen balance.



TABLE I

|                   | (1)     | (2)      | (3)             | (4)                          |
|-------------------|---------|----------|-----------------|------------------------------|
|                   | Glucose | Nitrogen | N $\times$ 5.50 | Glucose Util.<br>(3 minus 1) |
| Hypophysectomized | 0.64    | 0.40     | 2.20            | 1.80                         |
| Controls          | 2.34    | 0.67     | 3.69            | 1.26                         |

the glucose and nitrogen excretions of hypophysectomized and of normal dogs, both fasting.

Column 3 gives the glucose produced from the body protein breakdown assuming that each gram of protein nitrogen is equivalent to 5.5 gm. of glucose. In column 4 is given the glucose utilization by the tissues, i.e., the glucose produced (column 3) minus that which was excreted (column 1). Not all series show this difference but this is cited to show that glucose utilization may, at times, actually be higher in the hypophysectomized animals.

The study of anterior pituitary function by injections of extracts of the gland is complicated by the possible effects of the extracts on the adrenals and thyroid through the adrenotropic and thyrotropic hormones. To some extent, then, effects on carbohydrate metabolism may be secondary to the action on these glands. However, there is clear evidence that extracts of the pituitary act on carbohydrate metabolism without the intermediation of other ductless glands (43).

There seem to be two factors in the anterior pituitary which affect carbohydrate metabolism, one exerting its action soon after its injection and for a period of a day or two thereafter; the other producing an effect which persists indefinitely. The action of the former is brought about by injection of the whole gland extract and is evidenced by the rise of blood sugar of normal animals, the increase in glycosuria of partially depancreatized animals, and the counteracting of the huge glucose need of hypophysectomized rabbits. The factor acting for a longer period of time was discovered by Young (44, 45) who found that dogs given daily injections of crude pituitary extract of absolutely fresh glands for a week or so became permanently diabetic. These animals developed degenerative changes in the pancreatic islet tissue (46) and low insulin content of the pancreas.

#### Adrenal Cortex

In many respects the adrenal cortex acts on carbohydrate metabolism in a manner similar to that of the anterior pituitary. Adrenalectomy in fasting animals leads to depletion of the liver and muscle glycogen and to hypoglycemia (43) and there is a lower protein catabolism than in normal animals. Administration of

cortical extract to normal or adrenalectomized mice and rats causes an increase in liver glycogen and a rise in blood sugar (43). Long and Lukens (47) showed that adrenalectomy attenuates the diabetes of the depancreatized cat in a manner similar to hypophysectomy. In partially depancreatized rats adrenalectomy decreases the glycosuria and cortical extract injections increase it. The general condition of fasted hypophysectomized rats is improved by injection of cortical extract and at the same time they show an increase in the liver glycogen and blood glucose. The urine nitrogen is also increased. These findings might suggest that much of the effect of the anterior hypophysis on carbohydrate metabolism may be mediated through its adrenotropic action. However, anterior pituitary extract has a diabetogenic action (increased blood sugar and glycosuria) on adrenalectomized depancreatized animals (43) which shows that the extract can act directly without any secondary action by the adrenals.

Long et al. (43) find that nitrogen catabolism in rats is reduced after adrenalectomy and is increased in such animals by cortical extract. They conclude from this that one of the properties of the cortical hormone is a stimulation of protein catabolism and that the increased blood-sugar levels following its injection into animals is an expression of this effect. However, we may consider this point in the same way as in discussing the anterior pituitary. The increased protein catabolism may be the result of the decreased sugar utilization by the tissues, which results from the action of the cortical hormone. We have again the question of whether removal of the adrenals results in lower body protein conversion to glucose with subsequent hypoglycemia, or whether adrenalectomy brings about increased glucose utilization by the tissues and this decreases the breakdown of body protein and hence there is less new glucose formation.

Some workers have attempted to determine the protein catabolism of adrenalectomized animals by subjecting them to fasting and phloridzin and thereby straining the protein catabolism (48). They report that such animals break down less body protein than normal fasting phloridzinized animals. It is inferred that the loss of the adrenals interferes with the breakdown of body protein. There appears to be a more probable cause of reduced protein catabolism in these animals. These animals have all metabolic processes retarded, evidently because of very low blood sugar. The temperature is reduced (43). The oxygen consumption is low (49). Indeed many animals are near death. Why should one assume that the metabolic process of protein catabolism does not behave like other metabolic processes and be reduced? That it is the low blood-sugar level that retards metabolism is indicated from the results obtained on giving these

rats sugar. Oxygen consumption increases and the temperature rises. The giving of sugar actually increases the breakdown of body protein (48).

Additional support of the view that the increased protein metabolism is secondary to increased sugar utilization is found in the results of Long and Lukens obtained in depancreatized adrenalectomized cats. The following figures give the nitrogen excretion of their animals as given in table 2 of their paper.

| Experimental Condition              | Fasting<br>Nitrogen Excretion |
|-------------------------------------|-------------------------------|
| Normal, fasting                     | 0.6                           |
| Depancreatized                      | 1.4                           |
| Adrenalectomized and depancreatized | 0.6                           |

It is apparent that the adrenalectomy reduces the high protein catabolism of pancreatic diabetes to a normal level. Despite this normal protein breakdown most of their animals show hypoglycemia. In table 4 of their paper they report the blood sugars of 11 of their adrenalectomized-depancreatized cats after an overnight fast. Of the 11, 7 were markedly hypoglycemic, 2 had normal blood sugar values and 2 were hyperglycemic. The same animals were not necessarily reported in the two tables but the results are suggestive. If the hypoglycemic animals reported in table 4 had normal or slightly subnormal protein breakdown (which was the case for those reported in table 2), these animals must have had glucose utilization rates higher than normal since their blood sugars went to levels so much lower than that of normal fasting cats.

If, then, these animals have rates of glucose utilization that are normal, or higher, the lower results for nitrogen excretion are to be expected since we have removed the incentive for increased nitrogen catabolism.

#### Endocrines and the Protein Carbohydrate Relationship

We may sum up here the bearing that the endocrines have on carbohydrate and nitrogen metabolism. In the carnivora, removal of the pancreas results in a decrease in carbohydrate utilization and in an increase in body protein catabolism during fasting. These effects are reversed by supplying insulin. In herbivora, pancreatectomy brings out an inability to store carbohydrate but does not reduce to any marked extent the capacity to utilize glucose for current needs and does not bring about any increase in body protein catabolism during fasting. The removal of the pituitary increases the utilization of glucose and decreases a supernormal body protein breakdown when this is present. This effect is particularly evident in diabetes. The removal of the adrenal glands brings about results similar to those caused by hypophysectomy. Injection of the extracts of these glands usually produces effects opposite to those of removal of them.

If we accept the concept that increased utilization of glucose by the tissues results in lowering of the protein catabolism of these tissues, the known facts of endocrine function in intermediary metabolism can be greatly simplified. We need not suppose a distinct and separate protein action for each of the endocrines acting on carbohydrate metabolism. If this latter action operates, then the effect on protein metabolism would result from a physiological process common to all these situations. It is apparent that the blood-sugar level of itself cannot be the factor determining tissue protein breakdown. The blood sugar is high in depancreatized carnivora and there is a large breakdown of body protein. This latter can be brought to normal either by hypophysectomy or adrenalectomy which on the other hand occasion a very variable blood sugar level. The blood sugar is very low as a result of fasting and phloridzin and here there results a high tissue protein breakdown.

#### Summary of Endocrine Relationships

It is apparent that the endocrines play a very important rôle in regulating the mechanisms affecting the blood-sugar level and concerned with maintaining it at a proper level. Adrenalin releases glycogen when glucose is needed quickly. Insulin increases utilization of glucose particularly by storage routes, and restrains an excessive new formation of glucose from protein. The anterior pituitary and adrenal cortex inhibit the utilization of glucose by the tissues. The action of these two latter glands, under normal conditions restrains the otherwise large consumption of sugar by the body. When they are removed, the tissues, freed from their curbing action, consume greatly increased amounts of glucose. It seems, then, that the average body cell, freed of all hormone constraint uses a large amount of glucose. Evidence for this is seen in the high rate of sugar utilization of the hypophysectomized eviscerated animal (41) and of the ordinary cell grown in tissue culture (32). In the physiologically functioning subject this is ordinarily reduced by pituitary and cortical action. The insulin mechanism increases glucose utilization on occasions of large carbohydrate intake.

#### SUMMARY

Despite marked variation in feeding, the blood sugar is kept at a normal level by the proper regulation of tissue utilization, conversion of glucose to storage products, and new formation of glucose by the liver. These mechanisms are largely controlled by the endocrine system. When carbohydrate intake is high, glucose is stored as glycogen and fat as a result of insulin activity. In the post-absorptive state insulin activity decreases, thereby stopping storage, later allowing glycogen to be released and still later result-

ing in breakdown of body protein with resultant new formation of glucose. Glucose utilization by the tissues is increased during feeding (200-250 mg. per kg. per hour) and this is gradually cut down by fasting to 100 mg., or less, per kg. per hour. This control is independent of insulin and might well be effected by the anterior pituitary and adrenal cortex.

The living cells of the body, separated from all hormone activity, seem to have a very high rate of glucose utilization. In the body under physiological conditions, this rate is markedly curbed by the functioning of the pituitary and adrenal glands.

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# 'Spontaneous' Variability of Oral Glucose Tolerance

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**D**URING THE COURSE of an investigation of the carbohydrate metabolism of non-diabetic subjects we have been struck by the frequent occurrence of wide variations in the blood-sugar levels of individuals on repetition of the oral glucose tolerance test. Since this procedure is widely utilized under the impression of its consistency of results, it has seemed desirable to present our experience with it.

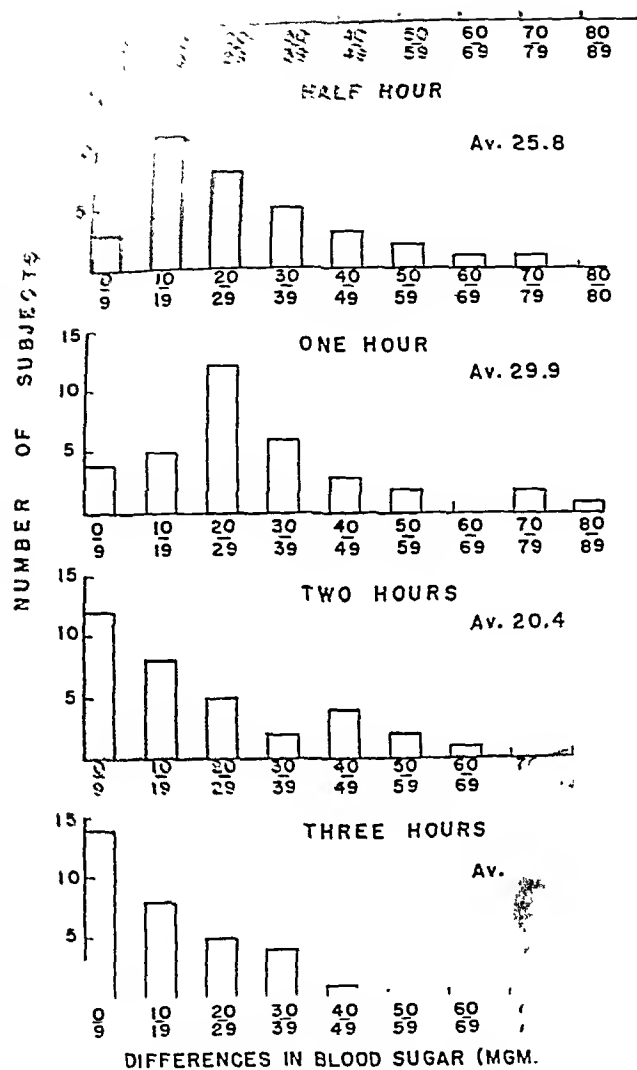
Despite the multiplicity of investigations in this field, there is a surprising dearth of information concerning the stability of this reaction in the individual subject and under comparable conditions. In a study of two normal subjects with blood samples taken every few minutes, Bock, Schneider and Giltert (1) found that on duplicate determinations there was a difference of 25 mg. per cent in one and 62 mg. per cent in the other at coincident points on the glucose tolerance curve. Glassberg's (2) series on 5 patients showed an average variation between two readings extending from 13 mg. per cent in a fasting state to 40 mg. per cent one hour after the ingestion of glucose. John (3), in a study of the glucose tolerance of children and adolescents, stated that the curve was stable insofar as the normal values did not, on repetition, exhibit the characteristic features found in diabetes mellitus. However, the three subjects on whom graphs were shown had differences at coincident points ranging from 10 to 45 mg. per cent. In a later paper (4), the average variation between duplicate readings one hour after the ingestion of glucose was 47 mg. per cent. Lennox (5) investigated the consistency of the glucose tolerance curve in 50 subjects, most of whom were epileptic; he gave detailed figures on 31 of these. His results also indicate wide variations, although of a slightly lesser extent than those of John (4). Hale-White and Payne (6), in their study on 8 normal young adults, found that there was considerable variation in the same individual on different days, as

shown in the rate and height of the rise of the blood sugar and the time taken for it to return to normal.

None of these investigations was performed on individuals on standardized diets and it is fair to assume that, with the known influence of dietary factors upon the type of curve, the variations found in the previous instances might have been lessened by the use of such diets. Hosters (7) stated that he did obtain consistent results in cases of diabetes mellitus on a fixed diet. On the other hand, Nielsen (8) performed 3 to 4 glucose tolerance tests on each of 8 non-diabetic individuals on a uniform diet and noted that the successive tests were on the whole fairly uniform with regard to approximately the same rise but that they differed rather markedly in the time of the rise. In addition, Soisalo (9) reported that in 17 healthy young subjects on a uniform diet, repetitions of the glucose tolerance test showed good agreement in 9 instances and marked divergence in the other eight. His conclusion was that the variations were as great after a standardized diet as otherwise.

The material to be presented in this report includes the glucose tolerance curves of 35 physically healthy male individuals. Thirty of these subjects suffered from schizophrenia but as the values did not differ appreciably from those of the other five normal subjects, nor from the figures obtained from the literature, it may be assumed that the results can be applied to non-psychotic normal individuals. All bloods (venous) were taken in a fasting state with the subjects lying quietly in bed. After a control sample of blood was drawn, 100 gm. of glucose dissolved in a glass of water was ingested. Blood was then obtained at periods of 30, 60, 120 and 180 minutes later. The tests were repeated in 28 of the subjects one week later and in the other 7 at intervals varying from 2 to 80 weeks. The average interval was 4.7 weeks. The diet was not standardized but it varied little from week to week in the institution. The analysis of the blood for sugar was determined by the Folin-Wu (macroalkalim-copper tartrate-colorimetric) method.

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1. DISTRIBUTION OF DIFFERENCES BETWEEN BLOOD SUGAR VALUES OBTAINED IN TWO GLUCOSE TOLERANCE TESTS AT THE FASTING AND ONE-HALF HOUR, ONE, TWO AND THREE HOURS AFTER INGESTION OF GLUCOSE; 35 SUBJECTS.

TABLE 2. AVERAGE DIFFERENCES BETWEEN SIMILAR POINTS ON TWO GLUCOSE TOLERANCE TESTS.

|          | No. of Cases | Interval Between Tests (weeks) |
|----------|--------------|--------------------------------|
| John     | 14           | 28                             |
| Lennox   | 31           | 14                             |
| Patients | 30           | 5                              |
| Normals  |              | 1                              |

TABLE 1 shows the average figures for the two glucose tolerance tests on the 35 subjects. The values are in general comparable to those found in the literature in normal individuals. The mean values for the second test tend to be slightly lower, a trend which has been previously noted by Lennox (5). However, the difference is not sufficiently marked to have any great significance.

Despite the general similarity of the mean curves there are marked variations between the individual

TABLE 1. MEAN BLOOD SUGAR VALUES OF TWO GLUCOSE TOLERANCE TESTS IN 35 SUBJECTS

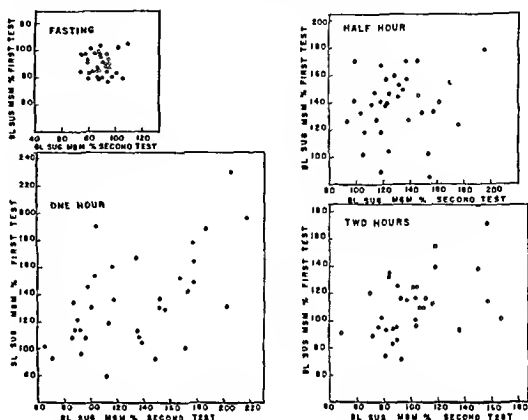
|             | Fasting (mg.%) | .5 Hr. (mg.%) | 1 Hr. (mg.%) | 2 Hr. (mg.%) | 3 Hr. (mg.%) |
|-------------|----------------|---------------|--------------|--------------|--------------|
| First Test  | 90             | 138           | 136          | 109          | 92           |
| Second Test | 89             | 131           | 133          | 102          | 87           |

pairs of tests. The average differences between similar points on the two glucose tolerance curves are seen in table 2. For the sake of comparison the values obtained by John (4) in adolescents and by Lennox (5) in normal and epileptic subjects are shown. In our

differences between the two readings is no greater than 9 mg, in 13 others between 10 and 19 mg, and in 3, from 20 to 29 mg. One-half hour after the ingestion of glucose, the differences begin to extend to higher levels, reaching the most marked divergence

scatter diagrams in figure 2. Here is shown the degree of relationship between the blood-sugar figures obtained in the two tests at the fasting level and at intervals of one-half hour, one and two hours after the ingestion of glucose. If the correspondence of one

Fig 2 SCATTER DIAGRAMS to determine the relationship between the values obtained in the first glucose tolerance test and those in the second test at the fasting levels and one-half hour, one and two hours after the ingestion of glucose, 35 subjects



at the 1-hour reading. At this time the most frequent variation between the two determinations lies between 20 and 29 mg, per cent. Subsequently, as the blood sugar levels fall their variability tends to decrease, although the 3-hour reading is still less con-

sistent with the other were of a high degree, the dots would scatter in a narrow zone from the lower left to the upper right. Of the four correlation graphs only the one representing the 1-hour reading shows any definite trend and this a not very good one owing to

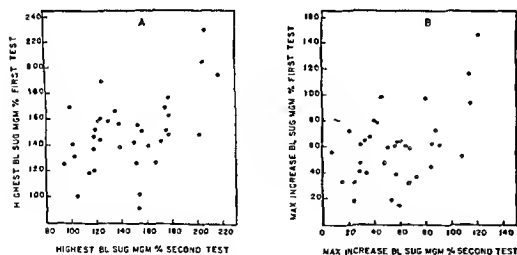


Fig 3 SCATTER DIAGRAMS to determine the relationship between the highest values of blood sugar obtained in two glucose tolerance curves (A) and the maximum increases from the fasting levels in the two curves (B), 35 subjects

sistent than the control values. It is evident that, at the lower levels of blood sugar, an individual may show a variation up to 30 mg (fasting) and under the stimulation of glucose ingestion, the inconsistency of the determinations may be as great as 90 mg. On this basis the reliability of any single value is slight.

The variation shown in figure 1 is not the result of a consistent upward or downward trend in the values. The differences are of a random nature as indicated by the general similarity of the two mean glucose tolerance curves in table 1 and also by the

wide scatter. In order to determine whether this relationship could be improved by taking into consideration the fasting level, the individual increases in blood sugar from the control to the one hour reading in the two tests were plotted against each other. This procedure did not improve the trend. Nor was it affected by taking this increase as a percentage of the control value. It is obvious, therefore, that any prediction that a given value will recur at a similar time in the glucose tolerance curve has a poor chance of fulfillment.

Since, to the clinician, the maximum level of blood sugar attained may be as important as the time at which it occurs, such maximum values were plotted against each other irrespective of their exact timing (fig. 3, A). The relationship was again very slight. Nor was the situation appreciably improved by taking into account the variation of the fasting blood sugar as in figure 3, B. Here the rise in blood sugar from the control to the maximum level in the first test was correlated with the similar figure in the second test. A marked scatter and only a slight trend was the result. The plotting of percentage increases from the fasting levels again failed to change the picture.

It is evident, therefore, that the variation in the blood-sugar curve following the ingestion of glucose is too great to be of any precise diagnostic value whether one takes identical points, maximal values or increases from the control levels. One must interpret with caution any changes following medication or treatment. It may be argued that such great variation may be attributed to the fact that the subjects were not on a standardized diet. The failure to obtain greater consistency on a fixed diet by Soisalo (9) and the fact that the institutional diet in this series was quite uniform from one week to the next casts some doubt upon the validity of this criticism. Moreover, the extent to which this is true necessarily complicates the procedure and in addition does not eliminate other reasons for the lack of consistency such as the variation in gastro-intestinal absorption and in the pancreatic and hepatic reactions (10) in the ingested glucose.

#### SUMMARY

The oral glucose tolerance test was investigated as a possible diagnostic feature for endocrinopathic

conditions. Repetitions of the procedure showed marked inconsistency in the curves. A review of the literature revealed that there had been few investigations in normal subjects of the consistency of this test. The material was therefore enlarged to include a total of 35 physically healthy male subjects in whom duplicate determinations were made within a short time. Analysis of the data showed that the average variation in the fasting level of blood sugar between the two tests was 9 mg. per cent and extended to 31 mg. per cent at the 1-hour reading with a maximum deviation at this point up to 90 mg. per cent. The relationship between the fasting, half-hour, 1-hour and 2-hour readings, respectively, in the two tests was very slight, the 1-hour reading showing the highest covariance. This inconsistency was not improved by comparing either the maximum levels attained in the two tests or the maximum increase in the blood sugar, irrespective of time. The variability of the test is so great that it has slight diagnostic value except in diabetes mellitus.

We wish to express our thanks to Miss Anna I. Walsh and Miss Cora G. Dyer for their careful determinations of the blood sugar values.

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# Comparison of Effectiveness of Various Methods of Administration of Insulin

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THE EFFICACY of the administration of insulin by various routes has been investigated repeatedly. Insulin has been given orally (1, 2, 3), in solution, by installation into the duodenum, jejunum, and ileum (4), and orally in alcoholic solution within keratinized capsules (5). Murlin's studies (6) showed that on the average 10 units of insulin given subcutaneously had an effect which approximated that of 800 units given orally. The effect was not always proportional to the dose. Komisarenko, et al (7) demonstrated that insulin was inactivated in the stomach in 15 minutes, in the duodenum in one hour, and in the colon in 2 hours.

Insulin also has been given intranasally (8), by inhalation of insulin spray (9, 10) by rectum, by vagina, and by absorption through the scrotal sac (11). Inunction also has been tried (12). By all of these methods insulin has had weak, doubtful, or frankly negative effects. Consequently, in clinical practice the subcutaneous or intravenous route of administration has continued to be used to the exclusion of all other methods.

Two methods remained which appeared to show a little more promise, namely, that of sublingual administration and of implantation. Preliminary experiments by Sacks (13) suggested that further studies of the sublingual method might be desirable. Certain steroid hormones have been given in this way with good effects.

Parkes and Young (14) in experiments on rabbits found that the hypoglycemic action of amorphous insulin pellets was only slightly more prolonged than that of a similar amount of insulin solution administered subcutaneously. Crystalline insulin pellets had a similar duration of action despite the fact that the tissue capsule around the pellet contained appreciable amounts of insulin.

Using depancreatized dogs, Mark, et al (15) found that pellets of crystalline zinc insulin with protamine were effective for as long as 100 hours. On examina-

tion 4 hours after implantation, the pellets were swollen; there was edema at the site of implantation.

Cutting et al (16) reported briefly on the effective use of pellets of cholesterol and insulin in depancreatized dogs. They observed a slow release of insulin during periods of as long as 13 days. The irregularities of absorption were too great to justify the trial of such pellets in the clinical treatment of diabetes.

This paper is a summary of experiments performed to determine the effectiveness of the sublingual administration of insulin, of the implantation of pellets made of insulin and cholesterol mixtures, and of the implantation of silver cylinders packed with crystalline insulin and open at the ends.

## Sublingual Administration

**Methods.** Experiments were made on 3 normal adult human subjects, one diabetic human being, and two normal adult dogs, to determine the effectiveness of this method of giving insulin. Blood sugars were determined by the Somogyi modification (17) of the micro Shafer-Hartman method.

The diabetic patient was carefully regulated with insulin and was fed a constant diet which was weighed to the fraction of a gram on balance scales. Food values were calculated. Previous blood sugar levels in this individual had been 148 mg per cent 2 1/2 hours post cibum, 133 mg per cent 4 hours post cibum, and 187 mg per cent, fasting. He was given food supplying constant quantities of available glucose at each corresponding daily feeding at 8 and 10 A.M., at 12 noon, and at 2 P.M. He received no insulin on 2 days, sublingual amorphous insulin solution on one day, and 20 mg and 40 mg of crystalline insulin (sublingual) on 2 days. On the day preceding the last sublingual dose of insulin he received 11 U (0.5 mg) of crystalline insulin subcutaneously. Blood sugars were taken at 8, 9:15, and 10 A.M., 12 noon, and 3 P.M. daily. Insulin was held against the sublingual area in an especially designed glass spoon. The spoon was held firmly against the tongue so as to prevent the mixing of more saliva than was sufficient for solution of the insulin. An area of 2.5 sq. cm. was ex-

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TABLE 1. SUBLINGUAL INSULIN ADMINISTRATION TO DIABETIC PATIENT  
Blood glucose, mg. per 100 cc.

| Time       | 4/27/42 | 4/28/42  | 4/29/42 | 4/30/42  | 5/1/42    | 5/2/42     |
|------------|---------|----------|---------|----------|-----------|------------|
| 8:00 A.M.  | 103     | 100<br>* | 96      | 96<br>** | 96<br>*** | 96<br>**** |
| 9:15 A.M.  |         |          |         | 115      | 107       | 124        |
| 10:00 A.M. | 115     | 124      | 120     |          | 72        | 112        |
| 12:00 N.   | 96      | 100      | 96      | 92       | 83        | 92         |
| 3:00 P.M.  | 100     | 96       | 96      | 96       | 92        |            |

\* 25 U of amorphous insulin, sublingual  
\*\* 2 mg. of insulin crystals, sublingual  
\*\*\* 11 U of crystalline insulin solution, subcutaneous  
\*\*\*\* 4 mg. of insulin crystals, sublingual

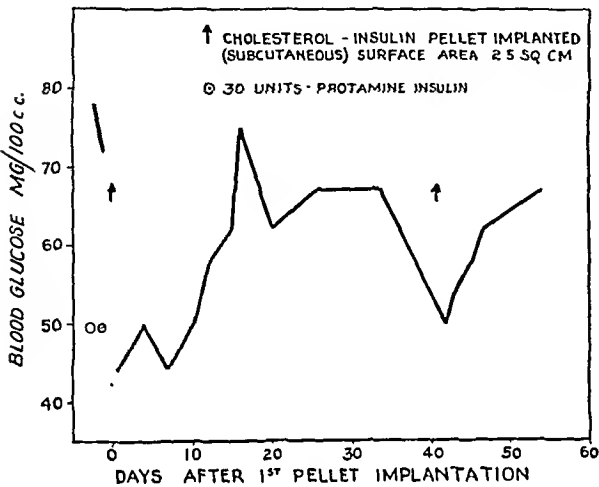
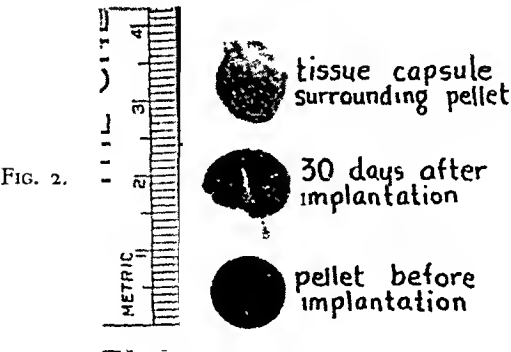


FIG. 1.

posed to the insulin for a period of 10 to 15 minutes. In the case of the normal human subjects, blood sugars were determined at hourly intervals during a 4-hour period when the subject was in the post-



absorptive state. In the dogs the blood sugars were determined one-half, 1, 2, and 3 hours after the administration of insulin. In two experiments on the dogs a solution of 20 per cent saponin was held against the sublingual area for 5 minutes immediately preceding the insulin application (1.2 mg. in 1 cc. water). In two experiments the insulin and saponin were applied simultaneously.

Results. Table 1 summarizes the results on the dia-

betic patient who showed a mild, though distinct, response to the subcutaneous insulin and no response to the doses given under the tongue. The normal human subjects and the normal dogs also showed no appreciable response to sublingual insulin. In the dog there was an unusually copious salivary secretion, particularly in the experiments using saponin. The use of saponin had no significant effect.

*Implantation of Insulin-Cholesterol Pellets and Silver Cylinders Packed with Crystalline Insulin and Open at the Ends*

The effective use of pellet implants of different hormone preparations suggested an investigation of this mode of administering insulin.

Methods. Normal adult dogs maintained on a constant diet were used. They were fed at 3 P.M. daily

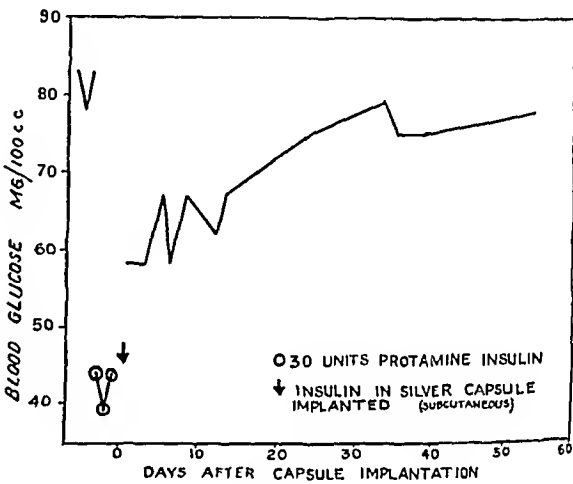


FIG. 3.

All excitement was carefully avoided. Blood was drawn from the saphenous vein when the dog was in the postabsorptive state. Normal blood sugars were determined at 2-hour intervals during the day, and at the same times following the subcutaneous injection of amorphous insulin. Doses of 4, 6, 8, and 12 u were given on different days to determine the response to varying amounts of the hormone. Protamine-zinc insulin also was tested.

After these preliminary tests, pellets composed of a mixture of 20 per cent insulin and 80 per cent cholesterol were implanted. The pellets weighed about 325 mg., had a surface area of 2.5 sq. cm., and were made by tightly packing a mold and hammering the material with 6 or more blows. The fact that the weight range of the pellets was small indicated a constant degree of packing. Silver cylinders (2 mm. in inside diameter  $\times$  100 mm., open at the ends) were firmly packed with about 30 mg. of crystalline insulin. In studies with crystalline albumen it had been determined that approximately 1 mg. of protein is released in 24 hours from tubes of this diameter. The

pellets and cylinders were sterilized by heating at 100° C for one hour on 3 successive days, and were implanted subcutaneously using local anesthesia.

**Results** The implantation of the insulin cholesterol pellets was followed by a marked decrease in blood glucose. The effect diminished steadily over a period of approximately 3 weeks and may have been completely absent thereafter. The fact that average blood-sugar levels for some time following were lower than the control levels suggested a more prolonged mild action. Figure 1 summarizes the results on one dog and is typical of those on the other animals similarly treated. The fact that the dog responded similarly following the second pellet implantation showed that there was no decrease in sensitivity to insulin. After several weeks the pellets were removed and were found to be surrounded by a capsule of firm tissue which on histologic examination showed a mass of granulation and young fibrous tissue typical of that forming around a nonirritating foreign body. The pellet inside the tissue capsule was moist, had become 'mushy,' and evidently was held in shape by the tissue surrounding it (fig. 2). The material, however, had marked insulin potency.

In one case in which there was no visible fragmenting of the pellet, the dog was dead the morning following implantation, apparently of insulin shock. The pellet was examined and appeared to be entirely firm and whole.

Following the subcutaneous implantation of the silver cylinders filled with insulin into the dogs, the blood sugar levels fell approximately to those observed following the injection of 20 to 30 U of protamine insulin. Figure 3 summarizes the results on dog M and is typical of the results obtained on the 5 dogs similarly treated. In one case the release of insulin was observed for only 2 days after implantation. When the cylinder was removed, the ends were found to be completely plugged with firm fibrin like clots. After 3 to 4 weeks the cylinders were removed and were found to contain appreciable amounts of potent insulin. On histologic examination the tissue surrounding the cylinders presented a picture similar to that which surrounded the insulin cholesterol pellet. It seems likely that the relatively large size of the insulin molecule is intimately connected with its lack of transmission through the fibrous capsule.

#### SUMMARY

1. Experiments were made on 3 normal human beings, one diabetic human subject, and two normal adult dogs to determine the effectiveness of the sublingual method of administration of insulin. Any effect of insulin administered in this way was so slight that this mode would appear entirely unsuitable for therapeutic use.

2. The implantation of pellets of insulin cholesterol (20 per cent insulin, 80 per cent cholesterol) into 4 normal adult dogs was followed by a marked drop in the blood sugar level. The insulin release gradually decreased until no definite effect of the hormone, as judged by the blood glucose level, was observed after 2 to 3 weeks.

3. A similar response was observed following the implantation of silver cylinders firmly packed with crystalline insulin and open at the ends.

4. In the case of both pellets and cylinders, the insulin effect was inconstant.

5. Examination of the tissue surrounding the pellets and cylinders showed a mass of granulation and fibrous tissue typical of that which forms around a nonirritating foreign body. This tissue apparently halted the insulin absorption.

We wish to thank Dr. F. B. Peck of Eli Lilly & Co., Indianapolis, Ind., for the crystalline insulin used in these experiments. We are indebted to Dr. J. Adelstein of the Strong, Cobb and Co. for the preparation of the insulin cholesterol pellets.

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# Diethylstilbestrol for Hemostasis in Functional Uterine Hemorrhage<sup>1</sup>

## [Oral Diethylstilbestrol]

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A WIDESPREAD and, not infrequently, uncritical usage of the non-hormonal estrogen, diethylstilbestrol, has followed its release into commerce by the Food and Drug Administration in the early Fall of 1941. Recently, diethylstilbestrol has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in *New and Nonofficial Remedies*.<sup>2</sup>

The practical value of diethylstilbestrol is enhanced by a), its low cost, b), the fact that it is active by mouth and c), its powerful estrogenic activity. These same factors can render it a harmful therapeutic agent if uncritically employed.

Recently our group reported (1, 2) that moderately small daily doses of diethylstilbestrol, when administered orally during the first half of the menstrual cycle, depressed corpus luteum function. No undesirable remote effects followed the moderate dosages employed by us. However, potentially unfavorable results from large doses, or from prolonged therapy, were envisioned. Diethylstilbestrol bids fair to be of particular clinical value in the treatment of certain functional gynecic aberrations. One of these is excessive or prolonged functional uterine bleeding.

Selection of the best manner of securing hemostasis in this condition often seems to be a difficult task for any clinicians. The relative merits of progesterone, androgenic and gonadotropic principles in this regard continue to be discussed at great length, while relatively little consideration is given to the estrogens. The gonadotropins now available have no hemostatic properties. Progesterone, on the other hand, actually increases bleeding instead of bringing about its cessation (3, 4). Androgenic principles possess hemostatic

properties but their use in woman is contraphysiologic and may result in severe depression of ovarian function, virilization, or both. These disturbing sequelae not only are undesirable, but they constitute needless traumatism inflicted by an unnecessary form of treatment.

We believe that the choice of the proper hemostatic agent in excessive or prolonged functional uterine bleeding should not be left to one's vagaries, but should be derived from the application of one of four simple rules. These rules have been developed for the purpose of individualizing treatment. Although exceptions are required occasionally, the general rules are as follows. a). For a patient 36 or more years of age, having excessive, prolonged or too frequent uterine bleeding, a complete curettage to rule out carcinoma is obligatory. b). For a patient under 36 years of age with qualitatively normal ovarian function (pregestational endometrium obtained at biopsy), and yet experiencing excessive, prolonged or too frequent bleeding, we elect to make a complete curettage to identify a submucous fibroid, an endometrial polyp, irregular shedding of the endometrium, or malignancy. c). For any gynecologic patient having severe and alarming uterine hemorrhage and grave anemia, we make a thorough curettage for gynecic diagnosis and for immediate hemostasis. d). For a patient under 36 years of age who is experiencing prolonged or excessive uterine bleeding, and yet who presents no urgent problem of hemostasis, hemostasis and regulation of flowing are obtained by estrogenic therapy.

As early as 1931 one of us (5) reported the use of hormonal estrogen (estrone) in controlling excessive uterine bleeding. Some six years later this therapeutic measure again was reported and recommended by one of us (3). The report of these latter studies was based upon several years of successful use of estrogens. Since then, members of our group have reported repeatedly (6-9) upon the rationale of employing estrogens to

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<sup>1</sup> Part of the expenses of these studies was defrayed by grants to one of us (E.C.H.) from the Research Council of Duke University and from Ayerst, McKenna and Harrison, Ltd., Montreal, Canada.

<sup>2</sup> Report of the Council: J. Am. Med. Assoc. 119: 632. 1942.

check excessive bleeding. Not only can hemostasis be obtained in the majority of instances, but subsequently cyclic bleeding can be secured. We have shown also (4, 9) that estrogens and progesterone administered cyclically and intramuscularly following hemostasis with estrogens (or curettage) may result in the re-establishment of normal ovarian-endometrial relationships. This has been observed to occur in 30 to 40 per cent of patients, our criteria for physiologic recovery being the continuation of cyclic bleeding from progestational endometrium and the subsequent intercurrent of pregnancies.

Recently our group described (10) the use of diethylstilbestrol in the regulation of excessive and prolonged uterine bleeding. It was found to be as effective as the hormonal estrogens in this regard. At the present time studies are being made of the results of cyclically administered diethylstilbestrol and anhydrohydroxyprogesterone with regard to its effects on the cyclic recurrence of bleeding and ultimate recovery of ovarian function. We have reported previously (11) that a schedule of cyclically administered oral therapy embracing hormonal estrogens and anhydrohydroxyprogesterone insured cyclic recurrence of bleeding, but that the percentage of recovery of ovarian function (17%) was low. Others (12), however, have described more encouraging results from the cyclic use of diethylstilbestrol and anhydrohydroxyprogesterone. Recovery of ovarian function with this oral therapeutic formula may prove to be of greater magnitude than that reported by us.

During our various studies concerning the effects of diethylstilbestrol upon the menstrual cycle and the anovulatory ovarian cycle some observations have been made upon the hemostatic properties of this substance. The present communication deals with these findings.

#### METHODS

Fifteen women who had prolonged or excessive uterine bleeding were treated with diethylstilbestrol<sup>3</sup> for hemostasis. Their ages ranged from 16 to 37 years, and averaged 25 1/2 years.

Diethylstilbestrol was administered orally in total daily amounts ranging from 2 to 6 mg for 6 days. One patient received 12 mg during 1 day. If bleeding was considerably checked, or hemostasis obtained within 6 days, the dosage was reduced to 4 mg daily for 1 week. Then the daily dosage was reduced again to 2 mg for 1 week providing withdrawal bleeding did not occur. In general, the therapeutic schedule, accordingly, covered a period of 3 weeks. However, the duration of individual treatments varied in length from 10 to 24 days.

<sup>3</sup> The diethylstilbestrol (Estrovene) was supplied by Ayerst, McKenna and Harrison, Ltd., Montreal, Quebec.

The continuation of therapy with diethylstilbestrol following hemostasis was designed to maintain hemostasis and, thereby, to regulate the bleeding cycle. Regardless of whether bleeding was due to estrogen withdrawal, or whether it occurred at approximately the expected time, estrogenic therapy, employing usually diethylstilbestrol, was begun on the 5th day of the next episode of bleeding and continued for 10 days, as a rule in daily doses of 1 mg.

Hemostasis was obtained by curettage if the patient could not tolerate diethylstilbestrol, or if it became apparent during the initial days of therapy that bleeding was not decreasing. Subsequent to curettage the patients were placed on cyclically administered diethylstilbestrol or cyclically injected estrogen-progesterone regime in order to establish and maintain regular bleeding.

The patients in this investigation received no other treatment for hemostasis except diethylstilbestrol.

Studies of the endometria were made by means of biopsies. These were obtained at the onset of episodes of bleeding. In general, the endometrium was not sampled until the first bleeding following hemostasis. Classification of the endometria was made by one of us (E.C.H.).

All patients had complete medical, gynecologic and endocrine surveys, including determinations of the basal metabolic rate and roentgenograms of the sella turcica. Particular attention was given to hematologic values.

#### DATA

There were 10 white and 5 colored women in the group. Nine were married, 3 of whom were colored. Two patients were aged 36 and 37 years, respectively. Each of them previously had had a curettage for diagnostic purposes as well as for hemostasis.

**Basal metabolic rates.** Values ranged from +11 to -18 per cent. Only 2 were below -10 per cent. These were -11 and -18 per cent.

**Hemoglobin levels.** Readings were based on 14.6 gm as 100 per cent. Those reported just prior to initiation of therapy were distributed as follows: 80 to 89 per cent, 3 patients; 70 to 79 per cent, 5 patients; 60 to 69 per cent, 4 patients; 50 to 59 per cent, 2 patients; 40 to 49 per cent, 1 patient.

**Duration of irregularities.** These ranged from 3 months to 16 years. The average was 5 1/2 years. The duration of the episode of bleeding at the time diethylstilbestrol was administered for hemostasis varied from 10 days to approximately 1 year. These were as follows: less than 1 month, 8 patients; between 1 and 2 months, 4 patients; between 2 and 3 months, 2 patients; approximately 1 year, 1 patient.

**Therapy for hemostasis on previous occasions.** Six of

the 15 patients had had some form of therapy for hemostasis in the past. Three of these had had curettages; 1 had received estradiol benzoate; 1 had received cyclically injected estrogens and progesterone; 1 had had a curettage followed by cyclically administered oral estrogens and anhydro-hydroxy-progesterone. The duration of cyclic bleeding following these therapies ranged in length from 1 to 24 months.

*Hemostasis with diethylstilbestrol.* Hemostasis was secured in 11, or 73 per cent, of the 15 patients. Bleeding stopped within an average of 4.4 days after initiation of treatment. The days on which cessation of bleeding occurred following initiation of therapy were distributed as follows: second day, 1 patient; third day, 4 patients; fourth day, 2 patients; fifth day, 2 patients; sixth day, 1 patient; eleventh day, 1 patient.

The daily dosages with which hemostasis was secured ranged from 2 to 6 mg. They were as follows: 2 mg., 2 patients; 4 mg., 2 patients; 6 mg., 7 patients.

Bleeding ceased within an average of 3.3 days after initiation of treatment with 6 mg., within 4.5 days with 4 mg., and within 7.5 days with 2 mg. dosage.

*Failure to secure hemostasis with diethylstilbestrol.* This was encountered in the case of 4 patients. Each patient reacted somewhat differently to therapy.

*Patient 1.* In this instance the therapeutic schedule was as follows: diethylstilbestrol, 6 mg. daily for 6 days; 4 mg. daily for the next 4 days followed by 2 mg. daily for 10 days. Bleeding checked during treatment with 6 mg. daily, but continued throughout the schedule. Curettage was made on the day following cessation of treatment. The patient was then started on a schedule of diethylstilbestrol, 2 mg. daily for 20 days. No bleeding occurred during this treatment.

*Patient 2.* The therapeutic schedule in this case was the same as that of *patient 1*. Bleeding checked during therapy with 6 mg. daily. It did not recur during therapy with 4 mg. daily. However, after 5 days of therapy with 2 mg. daily, bleeding reappeared, increased, and returned to its former character. The patient was curetted and was transferred to a regime of cyclically injected estrogen and progesterone upon which regular bleeding of normal proportions was re-established. This patient previously had been bleeding freely or spotting for approximately 1 year.

*Patient 3.* The patient entered our service with a hemoglobin of 50 per cent, having been bleeding excessively for 11 days. She was hospitalized and started on diethylstilbestrol, 6 mg. daily. At the end of the second day of therapy, bleeding had not been checked and the hemoglobin had fallen to 30 per cent. Curettement was made and the patient was started on a schedule of cyclically injected estrogen and progesterone.

*Patient 4.* This patient's basal metabolic rate was

— 18 per cent. She had been bleeding for 26 days. She was hospitalized and given 4 mg. of diethylstilbestrol on the day of admission. The following day a total of 12 mg. was administered. On the third day, the bleeding not having been checked and the hemoglobin becoming lower, curettage for hemostasis was performed.

*Withdrawal bleeding.* Five of the 11 patients who stopped bleeding under therapy experienced withdrawal bleeding. The time between cessation of therapy and the onset of flowing ranged from 1 to 3 days, and averaged 1.4 days.

#### DISCUSSION

In reviewing reports on the clinical use of diethylstilbestrol, one is impressed by the large number of postmenopausal women having normally dormant endometrium in whom uterine bleeding was induced. Relatively few investigators have employed diethylstilbestrol in excessive for hemostasis or prolonged uterine bleeding of the younger age group.

Palmer (13) usually obtained satisfactory results with a small dose (1 mg.) of diethylstilbestrol in controlling uterine hemorrhage. However, he encountered instances in which as much as 15 mg. daily was required for hemostasis. Wilson (14) found that 1 mg. daily caused no improvement in the bleeding of 2 patients. Pratt (15) reported on the use of diethylstilbestrol in 7 women who had excessive bleeding; 1 became worse under therapy; 2 were improved; 4 were satisfactorily controlled. Pratt observed in the case of a woman who had been bleeding for 24 days that oral administration of 5 mg. daily resulted in hemostasis 9 days after initiation of treatment. One of us (16) made the following statement in an editorial on diethylstilbestrol in this JOURNAL: "The hemostatic effect of diethylstilbestrol upon estrogenic (anovulatory) uterine bleeding should permit a cheaper and more practical regulation of bleeding than was possible with natural estrogens."

Rather than enter upon a discussion of the mode of action of estrogens in producing hemostasis in functional bleeding, a subject adequately covered in reports by members of our group, it would seem pertinent to draw upon observations made during this investigation for pointers which would be of practical value in the treatment of uterine hemorrhage with diethylstilbestrol.

Diethylstilbestrol apparently acts upon the capillary bed of the endometrium to produce hemostasis. In this regard, the action of the non-hormonal estrogen compares favorably with the hormonal ones.

Relatively small daily doses (2 mg.) administered orally can produce hemostasis, although the time required to be effective is longer than when larger doses are employed. We found that the daily dosage of 6 mg

was 70 per cent efficient in producing hemostasis. This percentage is not as high, perhaps, as we have obtained with injected hormonal estrogens. Our group has not employed diethylstilbestrol intramuscularly. Results from this mode of administration might prove equally as good as those following hormonal estrogens. However, the low cost of therapy and the convenience of the treatment to both patient and physician warrant the continued oral use of diethylstilbestrol.

Doses larger than 6 mg. daily were not employed except in the one instance in which 12 mg. were given during 1 day. We doubt seriously that larger doses would prove much more efficient, or that larger doses would have brought about hemostasis in the four reported failures. We believe that hemostasis obtained in from 2 to 5 days in ambulatory patients with a total daily dose of 6 mg. should prove satisfactory to the patient and physician as well.

The patient, whether out patient or hospitalized, who is to receive diethylstilbestrol orally for hemostasis should be supervised closely during therapy. The physician should not prescribe this form of treatment to the out-patient without giving careful instructions. Changes in the character of flowing should be observed by the patient. An increase in the amount of bleeding should be reported to the physician. Evidences of poor tolerance to diethylstilbestrol need not be anticipated, necessarily, but may be expected. Patients who respond to treatment should be watched following cessation of therapy in order that possible withdrawal bleeding may be dealt with promptly. If this occurs, additional treatment cyclically administered should be given to re-establish regular bleeding periods and, finally, if possible, recovery of ovarian function.

The only patient who had a basal metabolic rate considerably below normal limit failed to respond to treatment with diethylstilbestrol. This result may be significant since we have found that, in general, patients with a low basal metabolic rate responded better to treatment after stabilization with thyroid substance.

No common denominator for failure was found for

those patients who failed to stop bleeding under therapy with diethylstilbestrol.

#### SUMMARY

The oral administration of diethylstilbestrol, in daily doses ranging from 2 to 6 mg., to 15 women who had prolonged or excessive uterine bleeding, produced hemostasis in 11 individuals in from 2 to 11 days. The average time required for hemostasis was 4.4 days.

Of the dosages employed, that of 6 mg. was found most effective. Hemostasis occurred in from 2 to 5 days with this dosage, averaging 3.3 days. Smaller daily dosages secured hemostasis, but required a longer time.

Dosages of diethylstilbestrol larger than those employed in this investigation, or intramuscular administration, are thought unnecessary in view of the satisfactory results obtained in this study.

The effects of the non hormonal estrogen, diethylstilbestrol, after oral administration, compare favorably with those obtained by the intramuscular administration of hormonal estrogens in securing hemostasis in excessive or prolonged functional uterine hemorrhage.

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# Rationale of Estrogenic Therapy in Functional Dysmenorrhea<sup>1</sup>

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ESTROGENIC THERAPY for dysmenorrhea has been endorsed by many investigators. The rationale for its use, however, still is based on theory. Some clinicians believe that menstrual pain is a manifestation of an estrogenic deficiency, others claim that an excess of progestin is the exciting cause. Estrogenic therapy is used generally by those who hold either of these views, either as complementary therapy or as a contraphysiologic approach designed to override corpus luteum function. There is another group of workers who employ progesterone on the basis that the pain results from an excess of estrogen and presumably from a deficit in progestin production.

Systems of therapy based on these theories have been described as yielding varying degrees of relief but, as yet, no satisfactory explanations have been offered of the pharmacologic actions which produce desirable symptomatic responses. The alleviation of symptoms is usually regarded as proof of the correctness of whichever theoretical basis was postulated.

Since a recent study by members of our group (1) included an extensive review and summary of the literature on dysmenorrhea, these will not be repeated. However, Boynton and Winther (2) have but lately stressed the importance of the psychogenic factor in the etiology of dysmenorrhea. Dysmenorrheic patients were treated by them with comparatively small oral doses of an estrogen (estriol glucuronide) during the last half of the cycle. The results of this therapeutic schedule and the control placebo therapy were equivocal.

Our group readily admits the magnitude of the psychic element in dysmenorrhea. In fact, we have hesitated to predicate the existence of a functional endocrinopathy in dysmenorrhea. This present communication offers, however, observations made dur-

ing a broader investigation of the effects of estrogenic therapy on ovarian and endometrial functions (3-5), which seem to rationalize the employment of estrogenic therapy in dysmenorrhea.

## METHODS

For this study 18 women were investigated. Their ages ranged from 16 to 30 years and averaged 23.9 years. They complained of severe grades of dysmenorrhea which began at menarche or shortly thereafter.

Each patient received thorough medical, gynecologic and endocrine surveys including determinations of the basal metabolic rate and roentgenograms of the sella turcica. These surveys revealed no obvious causes for the dysmenorrhea.

Three hormonal estrogens (estradiol, estrone and estriol) and a non-hormonal estrogen (diethylstilbestrol) were employed in treating these patients. Estradiol and estrone were administered intramuscularly, estriol and diethylstilbestrol were given orally.

Estradiol was given during the first half of 7 cycles to 4 patients, i.e., from the 5th to the 14th days inclusive; the dipropionate<sup>2</sup> in total doses of 15 mg was given during 5 cycles and the benzoate<sup>3</sup> ester in total doses of 6 mg. was employed during 2 cycles.

Estrone<sup>4</sup> was administered to 8 patients during 15 cycles in total amounts ranging from 0.67 to 4.67 mg (20,000 to 140,000 I.U.). It was employed during a), the first half of 11 cycles, b), during the last half of 2 cycles, i.e., from the 15th to 24th days inclusive, and c), during both halves of 2 cycles, i.e., from the 5th to 24th days inclusive.

Estriol glucuronide<sup>5</sup> was administered to 9 patients

<sup>2</sup> Estradiol dipropionate (Di-ovocylin), supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

<sup>3</sup> Estradiol dipropionate (Progynon-B), supplied by Schering Corp., Bloomfield, N. J.

<sup>4</sup> Estrone (Theelin), supplied by Parke, Davis and Co., Detroit, Mich.

<sup>5</sup> Estriol glucuronide (Emmenin), and diethylstilbestrol (Estrobene), supplied by Ayerst, McKenna and Harrison, Ltd., Montreal, Quebec.

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<sup>1</sup> Part of the expenses of these studies was defrayed from grants to one of us (E.C.H.) from the Research Council of Duke University, from Ayerst, McKenna and Harrison, Ltd., Montreal, Canada and from Schering Corporation, Bloomfield, N. J.

during 20 cycles in total amounts ranging from 7,000 to 48,600 oral units. It was given during both halves of 17 cycles, in the first half of 1 cycle and during the last half of 2 cycles.

*Diethylstilbestrol*<sup>5</sup> was given to 6 patients during 17 cycles. It was given uniformly in daily doses of 1 mg. during the first half of the cycles.

Endometrial biopsies were obtained from every patient prior to initiation of therapy and from a number of them during and after therapy. The endometrial tissue was obtained within the first 24 hours after the onset of bleeding. Classification of the responses was made by one of us (E.C.H.)

The cycles were graded according to the severity of the dysmenorrhea described by the patients. These grades were 0, no pain, 1+, slight pain, 2+, moderate pain, 3+, severe pain, 4+, very severe pain.

Data upon the relation of the onset of dysmenorrhea to menarche, and upon the kind, severity, and duration of the pain were analyzed.

#### DATA

Data on the initial onset of dysmenorrhea were secured from 17 of the 18 patients studied. Eleven, or 65 per cent of these 17 related this to menarche, while 6, or 35 per cent, described its origin as occurring from 1 to 4 years after menarche. The age for the menarche ranged from 11 to 17 years and averaged 13 years. The age of the patients at the onset of the dysmenorrhea ranged from 11 to 17 years and averaged 14 years.

The onset of pain occurred on the first day of bleeding in 13 patients, 1 day premenstrually in 1 patient, 2 days premenstrually in 3 patients, and 7 days pre-

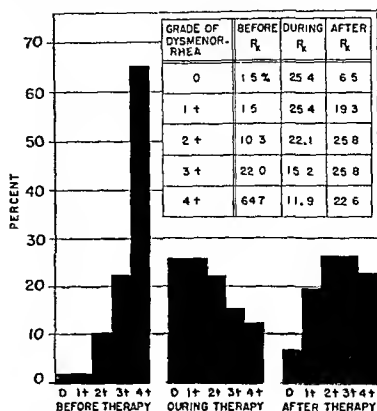


FIG 1. PERCENTAGE DISTRIBUTION of various grades of dysmenorrhea in the total numbers of cycles studied before and after estrogenic therapy

menstrually in 1 patient. The onset of pain and of bleeding were concomitant in 8 patients.

The duration of discomfort ranged from 3 hours to 10 days and averaged 3.7 days. The mode was 4 days.

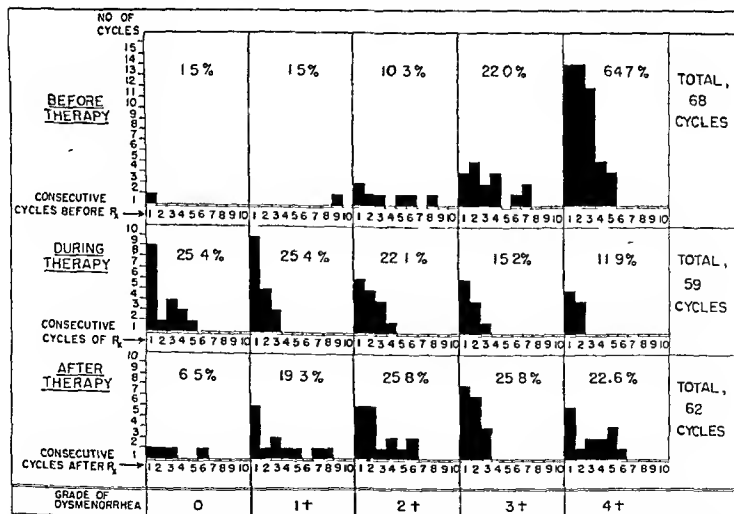


FIG 2. PERCENTAGE DISTRIBUTION of various grades of dysmenorrhea arranged according to consecutive cycles of study



In most instances, the pain ended on the 2nd or 3rd day of bleeding.

The most severe pain occurred on the first day of bleeding in 16 patients. The pain was constant and

quadrant pain in 1; breast pain in 3; headaches in 3; fatigue in 3; generalized aching in 1; edema, urticaria and diarrhea in 1; nausea and vomiting in 1 patient.

A total of 189 cycles was studied, 68 before ther-

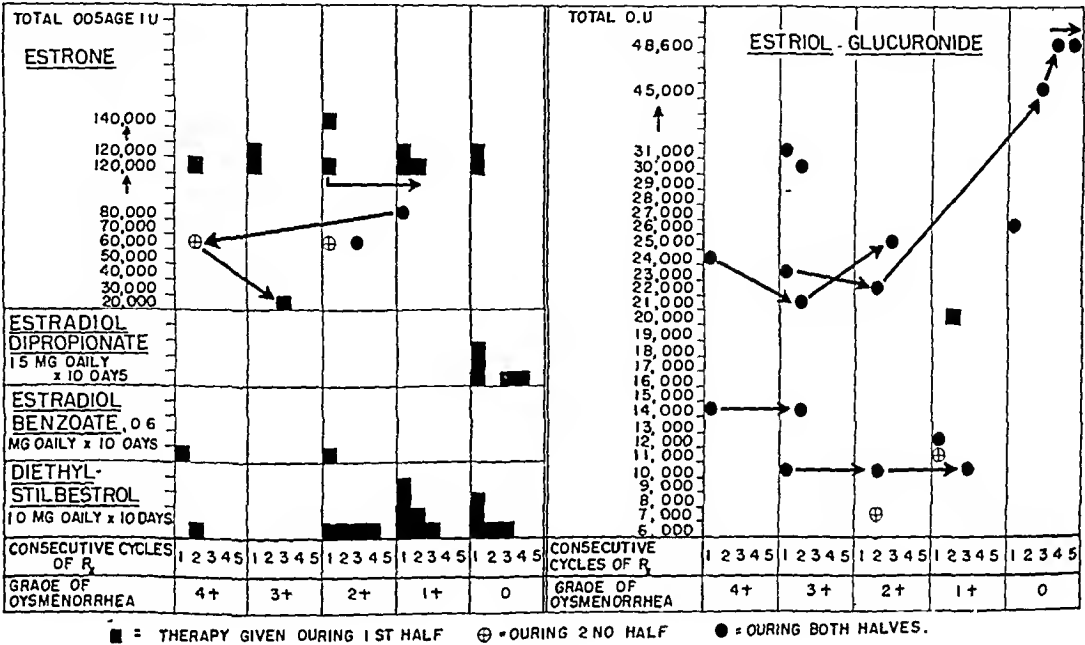


FIG. 3. RELATIONSHIPS OF VARIOUS ESTROGENIC THERAPIES, with regard to dosages and the time of administration during the cycle, and the various grades of dysmenorrhea in consecutive cycles of study. Arrows connect consecutive cycles of treatment and the associated grade of dysmenorrhea of individual patients. Block graphs correlate quantitatively the number of patients who received therapy during the first half of the cycle with the number of consecutive cycles studied.

without marked fluctuations in the remaining 2 patients. Thirteen patients described the pain as being intermittent and cramping, while 5 of them described an aching pain. The pain was chiefly lower abdominal or suprapubic in location in 16 instances and was generalized throughout the abdomen in 2 instances.

Secondary locations of pain and additional menstrual molimina were distributed among the patients as follows: none in 5; low back pain in 7; right, lower

quadrant pain in 1; breast pain in 3; headaches in 3; fatigue in 3; generalized aching in 1; edema, urticaria and diarrhea in 1; nausea and vomiting in 1 patient. A total of 189 cycles was studied, 68 before ther-

TABLE I. RELATION OF DYSMENORRHEA TO ENDOMETRIAL RESPONSES

| Grade of Dysmenorrhea             | 0 |    |   |   | 1+ |   |    |   | 2+ |   |    |   | 3+ |   |    |   | 4+ |   |    |   |
|-----------------------------------|---|----|---|---|----|---|----|---|----|---|----|---|----|---|----|---|----|---|----|---|
| Endometrial Response <sup>1</sup> | E | E+ | M | P | E  | M | M+ | P | E  | M | M+ | P | E  | M | M+ | P | E  | M | M+ | P |
| Therapy                           |   |    |   |   |    |   |    |   |    |   |    |   |    |   |    |   |    |   |    |   |
| Estradiol benzoate                |   |    |   |   |    |   |    |   |    | 1 |    |   |    |   |    |   |    |   |    |   |
| Estradiol dipropionate            | 3 |    |   | 1 |    |   |    |   |    |   |    |   |    |   |    |   |    |   |    |   |
| Diethylstilbestrol                | 3 |    |   |   | 3  |   |    | 1 | 1  |   | 1  | 2 |    | 2 |    |   | 1  | 1 |    |   |
| Estrone                           |   |    |   |   |    | 3 |    |   |    | 2 |    |   |    | 1 |    |   |    |   |    |   |
| Estriol                           |   |    |   |   |    | 1 |    |   |    | 1 |    |   |    | 1 |    |   |    |   |    |   |
| Follow-up after therapy           |   | 1  | 1 |   |    |   | 1  | 1 | 2  | 4 |    | 1 | 1  | 3 |    | 1 |    |   |    | 2 |
| Group totals                      | 6 | 1  | 1 | 1 | 3  | 4 | 1  | 2 | 3  | 8 | 1  | 3 | 1  | 6 | 1  | 1 | 1  | 2 |    | 2 |
| Grand totals                      | 9 |    |   |   | 10 |   |    |   | 15 |   |    |   | 9  |   |    |   | 5  |   |    |   |

<sup>1</sup> Classification of endometrial responses: E, moderate estrogenic response; E+, marked or hyperestrogenic response; M, moderate, irregular (patchy) progestational; M+, marked, irregular (patchy) progestational; P, normal progestational.

secutive cycles of therapy Table 1 gives the gradation of dysmenorrhea in relation to the endometrial findings as related to the various types of therapy All biopsies taken before therapy were progesterational in character

No ill effects resulting from therapy were observed or reported by the patients

#### DISCUSSION

It is evident from the data presented in figure 1 and 2 that marked relief from dysmenorrhea often occurred during treatment This is apparent in a large proportion of the first treatment cycles These data indicate also that relief from symptoms persisted in a number of instances after discontinuation of treatment Following cessation of therapy, however, there was a general tendency for the dysmenorrhea to return to the pretreatment level of pain

While there was relative freedom from pain in 13 per cent of the cycles studied before therapy, there were marked grades of relief in 73 per cent of the cycles during therapy and in 52 per cent of the cycles following the cessation of therapy Of these, there was complete absence of pain in 2 per cent of the cycles before treatment, in 25 per cent during treatment and in 7 per cent of the cycles studied after treatment

The dosages of the various estrogens employed and the manner of their administration were apparently definite factors in the alleviation of symptoms From the data in figure 3 it is apparent that therapy during the first half and during both halves of the cycle was effective in securing relief from pain These data indicate, but do not show conclusively, that results are more efficacious than when therapy is administered during the last half of the cycle alone Larger dosages proved more effective than smaller ones Estradiol dipropionate and diethylstilbestrol were given in the largest dosages and yielded prompt relief from pain in the greatest percentage of treatment cycles During treatment with estrone and with estril glucuronide, which were used in the smallest dosages, there was definite evidence of a carry-over and summation of effect in consecutive cycles of therapy

Therapy in one patient was followed by alterations in the character, time of onset and duration of dysmenorrhea For 3 consecutive cycles, treatment with diethylstilbestrol was given this patient Symptomatic relief was noted in every cycle during treatment Prior to therapy, pain characterized by lower abdominal cramps appeared 3 to 4 hours before flowing and was most severe with the onset of bleeding Following cessation of therapy, pain described as a severe pelvic ache occurred only on the day prior to the onset of flowing In the case of another patient, who had received therapy with estrone during 2 cycles, with

relief from symptoms, the onset of dysmenorrhea was changed from 1 day prior to flowing to 3 or 4 days premenstrually There were no other alterations in symptoms This patient was studied through 6 consecutive cycles following discontinuation of therapy Dysmenorrhea in these cycles was graded as 1+, 1+, 2+, 4+, and 4+, respectively.

That therapy apparently was able to change the character and periodicity of dysmenorrhea is interesting and it seems to indicate a specific relationship A similar relationship is probable in the case of one patient who reported continued marked relief following the cessation of therapy During 8 consecutive post-treatment cycles the dysmenorrhea was graded as 2+, 3+, 1+, 1+, 1+, 0, 1+, and 1+, respectively

The data presented in table 1 show clearly that there is no constant relationship between the type of endometrium from which bleeding occurs, whether estrogenic or progesterational, and the presence or absence of dysmenorrhea These data indicate also that, when relief from dysmenorrhea during therapy was associated with the occurrence of bleeding from an estrogenic type of endometrium, estrogens had been administered in the larger dosage schedules

This investigation, accordingly, raises the question as to how estrogens act to relieve dysmenorrhea The concept that relief is brought about by the over-riding of ovulation or corpus luteum function does not seem tenable An estrogenic endometrial response may be a matter of higher estrogenic dosage and its intercurrent is not necessarily in itself a factor in the relief of pain

In order to answer this question another question should be faced first What kind of pain characterizes dysmenorrhea? Dysmenorrhea is, first of all, pain of the sympathetic type Leriche (6) set up the criteria for this type of pain in contradistinction to the pain of the cerebrospinal type The latter is fixed and localized and has precise anatomical limits, while the former is more diffuse, of a spreading character, of irregular distribution, readily effecting and affected by the mental state and emotions of the patient Leriche also showed that pain of either type has a sympathetic component and that, if this be blocked out by surgery or local anesthesia, the pain will be relieved without demonstrable effect on any sensory mechanism in the region where the pain has been

This being so, and knowing that estrogens relieve dysmenorrhea, what autonomic effects do estrogens have? Reynolds (7) has shown that estrogens have a parasympathetic action mediated by inhibition of acetylcholine esterase Here we have a mechanism whereby the sympathetic component of dysmenorrheic pain can be blocked out by antagonistic action of the parasympathetic From this we may say

that dysmenorrhea is a functional condition brought about by a relative deficiency of estrogen which results in overactivity of the sympathetic nervous system characterized by the production of vasoconstriction and pain.

We are at once faced with the objection that numerous reports in the literature indicate that progesterone as well as testosterone relieves dysmenorrhea. Neither has any known autonomic action. This is true but it is also a fact that both have definite vascular effects and whether the vasoconstriction is overcome by antagonism of the sympathetic or by direct action to produce vasodilation, the end result is the same. Our group has shown (8) that progesterone will cause a fall in blood pressure by arteriolar dilation. Progesterone, testosterone and also desoxycorticosterone given in relatively large doses will produce vascular changes through alterations in capillary permeability (9). It is common knowledge that the vasodynamic drugs exert a beneficial influence on dysmenorrhea. There is even some indication that nicotinic acid, given in doses which produce generalized flushing, will relieve dysmenorrhea.

Progesterone and estrogens administered concomitantly have a very powerful vascular action (9, 10, 11). Gillman (9) has demonstrated that the amounts of estradiol and progesterone required to produce vascular changes in the uterus of the rabbit are inversely proportional, the greater the amount of estrogen used, the less the progesterone required, and vice versa. On the basis of this work, then, an important factor in the production of the vascular changes in the endometrium may be the ratio of estrogen to progesterone.

#### SUMMARY

Three hormonal estrogens, estradiol, estrone, and estriol and a non-hormonal estrogen, diethylstilbestrol, were employed in the treatment of functional

dysmenorrhea of 18 women whose ages ranged from 16 to 30 years. The total dosages of these substances per cycle of therapy ranged as follows: estradiol benzoate, 6 mg.; estradiol dipropionate, 15 mg.; estrone, 0.67 to 4.67 mg.; estriol glucuronide, 7000 to 48,600 oral units; diethylstilbestrol, 10.0 mg.

A total of 189 cycles was studied; 68 prior to therapy, 59 during treatment, and 62 after cessation of therapy. Estrogenic therapy was found to be effective when administered in adequate amounts during the first half or during both halves of cycles. During therapy there was complete absence of pain in 25 per cent and marked relief in 60 per cent of the cycles studied. After cessation of therapy, there was complete absence of pain in 5 per cent and marked relief in 28 per cent of the cycles studied.

No causal relationship was found between the absence or presence of dysmenorrhea and the type of endometrium from which bleeding occurred.

The concept that dysmenorrhea arises as a vascular pain and the mechanisms of pain production and relief were advanced and discussed.

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# Clinical Experiences with Oral Ethinyl Estradiol

## [Oral Therapy for Menopause]

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TO DATE there have been two reports (1, 2) in the literature of the clinical use of ethinyl estradiol benzoate as replacement therapy. This brief report is to summarize our experiences over a period of twenty three months in the use of ethinyl estradiol<sup>1</sup> for treatment of the menopause.

### SUBJECTS

There were 18 women, all of whom had typical menopausal complaints including hot flashes. No patients were included in this study who did not experience flashes because it was felt that the disappearance of these would more clearly indicate subjective improvement.

The average age was 48 years (range 36-63 years). Two 24 hour urine specimens were collected and assayed for estrogens and 17 ketosteroids. If the results of the assays did not check, additional aliquots were assayed until constant results were obtained. The urines were hydrolyzed, and extracted by the method of Hershberg and Wolfe (3), fractionated by the method of Gallagher et al (4). Specimens were assayed for estrogenic values by injections of an aqueous suspension in divided doses into 15 ovariectomized mice. Assays for 17 ketosteroids were made by the Friedgood Whidden (5) modification of the Zimmerman method using a Cenco spectrophotometer.

### METHOD OF ADMINISTRATION

Both plain and enteric coated tablets were used. No difference was noted in their effectiveness. Because of toxic reactions occurring during the early days of experimental use of diethylstilbestrol, a very conservative method of treatment was outlined when ethinyl estradiol was first used. After some experience it was found that one 15 mg tablet three times

a day for 3 days, twice a day for 2 days, and then one daily produced no toxic symptoms. The full estrogenic effect was delayed in some patients by this dosage. Further, it was found that in many instances when initial doses of 30 to 45 mg daily were necessary, the patient could ultimately take 15 mg every other day and in some instances every third day and keep the symptoms under control. Careful records of the results of treatment extend over a period of from 2 to 13 consecutive months.

To remove the psychological benefits of therapy phenobarbital, grains one half twice daily, were substituted for ethinyl estradiol. In all instances when this was done, the symptoms returned.

Six cases are reported in detail because of the interesting features encountered.

### CASE REPORTS

**Case 1, E S**, age 56, married, para 1, grav 1. Menarche began when the patient was 17 years old. The menses are regular, occurring every 28 days and are normal in duration and amount. The flashes have increased in intensity over the last 3 to 4 years and the patient has 10 to 12 sweats per day. There has been a definite loss of libido.

Urine analysis showed 5.2 and 3.5 micrograms of estrone, respectively, in the two 24 hour specimens. Values for the 17 ketosteroids were 10.2 and 7.5 mg, respectively for the two 24 hour urine specimens.

Ethinyl estradiol was prescribed as follows: 15 mg three times a day for 3 days, 15 mg twice a day for 2 days and beginning on the 6th day, 15 mg daily. Treatment was begun December 1, 1940. On December 12 the patient reported no improvement and the prescription was changed to 30 mg daily for 3 weeks. At the end of this time, January 2, 1941, the flashes were reduced in number to 5 a day. The prescription was continued and on February 11, after 40 days of therapy, the patient reported that she was less nervous and that flashes occurred but 3 to 4 times per 24 hours. On February 28, after 8 weeks of therapy with 30 mg daily the patient reported slight nausea during the day but that the flashes were reduced to 3 per 24 hours. The dosage was reduced to 15 mg daily on March 21, after 3 weeks of therapy with

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<sup>1</sup>The ethinyl estradiol benzoate was supplied by Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J.

this dosage the patient reported the flashes had increased to as many as 5 to 10 daily and that the nausea had continued. The nausea improved when the medication was omitted for a 2-week period when .15 mg. was again prescribed. On June 19, 1941, the patient reported she was much improved and had gained 24 pounds in weight since September, 1940. On July 31, she complained of soreness of the vagina which disappeared when she omitted the medication for 10 days. She had previously occasionally experienced this irritation when not taking the ethinyl estradiol. The flashes increased in number when medication was omitted. On September 11, 1941, medication was omitted because of soreness of breasts until October 7 when she reported 4 to 6 flashes daily and that the soreness of the breasts had disappeared. Ethinyl estradiol, .15 mg. daily was again prescribed. On April 28, 1942 the dosage was reduced to .05 mg twice a day. At the last report, May 28, 1942, there were no symptoms of toxicity. In summary, the results in this patient were excellent.

*Case 2, M. E., age 47.* This patient experienced difficulty in breathing, faintness and a sensation of constriction of the throat. The menses recurred regularly at 30-day intervals, lasting 4 to 5 days; flow normally was quite profuse. The patient reported she was nervous at this time.

In August, 1941, therapy with diethylstilbestrol was started. Severe nausea and 'hives' resulted so that therapy was discontinued.

Urine analysis showed 3.8 and 2.8 micrograms of estrone in the two 24-hour specimens. Values for the 17-ketosteroids were 8.2 and 10.0 mg., respectively.

On December 12, 1941, the following schedule of dosage with ethinyl estradiol was initiated. For 3 days, .05 mg. 3 times a day; for 2 days, .05 mg. twice a day, and .05 mg. daily thereafter. Four days later, December 16, the patient reported she felt better generally, but that she was experiencing slight nausea and eructations after taking the medicine for this period of time. She stated she had always had a 'weak stomach.' The dosage was reduced to .05 mg. per day. The next day she developed urticaria. The medication was stopped.

The results in this case were poor. A total dose of .70 mg. of ethinyl estradiol produced urticaria and nausea.

*Case 3, L. K. P., age 52.* In October, 1939, the patient received radium therapy for metrorrhagia. Six weeks later she experienced hot flashes and increased nervousness. Estrone in dosages progressing from 2000 to 5000 to 16,000 R. U. every other day afforded some relief. In September, 1940, the patient was having 12 to 15 hot flashes daily and was receiving 6000 R. U. of estrone every other day. The physical findings were normal.

Urine analysis showed 10.7 and 12.2 micrograms of estrone in the two 24-hour specimens. Values for the 17-ketosteroids were 7.5 and 7.5 mg.

On the basis of the assay the patient was given testosterone propionate, 25 mg. every 5 days until she had received 6 doses. There was no change in the number of the flashes. Therapy with ethinyl estradiol, .15 mg. twice a day for 25 days was instituted. Marked improvement resulted. Later the patient reported that .15 mg. every other day was sufficient to control the symptoms. As of

February, 1942, she reported continued improvement in general health and no flashes.

The results in this case were excellent and there were no toxic symptoms.

*Case 4, R. W., age 50.* In May of 1940 the patient had received roentgen-ray therapy for uterine fibroids. The last menses occurred in July, 1940, and since that time the patient had experienced hot flashes, excessive perspiration and an increased degree of nervousness and fatigue. Estrone in large dosages had failed to improve the general health or to control the hot flashes. The physical examination revealed nothing of significance.

Urine analysis showed 4.3 and 4.1 micrograms of estrone, respectively, in the two 24-hour specimens. The values for 17-ketosteroids were 6.0 and 7.7 mg., respectively.

On December 12, 1940, ethinyl estradiol, .15 mg. three times a day was prescribed. After 4 weeks of this therapy there was no improvement. The use of other estrogenic substances orally and parenterally likewise failed to alleviate the symptoms.

The results in this instance were poor. Apparently there were no toxic effects.

*Case 5, H. W., age 30.* For the past 2 years there has been an increase in nervousness, hot flashes, as many as 1 to 3 daily, and a loss of libido. The physical examination failed to reveal any significant findings.

Urine analysis showed 3.3 and 2.2 micrograms of estrone, respectively, in two 24-hour specimens. The values for 17-ketosteroids were 5.7 and 6.2 mg., respectively.

On January 22, 1941, the patient was given ethinyl estradiol, .15 mg. daily, until the present time. In December, 1941, the patient reported the flashes had decreased, that she had gained in weight and was less nervous. No toxic symptoms have appeared.

*Case 6, M. V. V., age 53.* Following cessation of menses 3 years previously, the patient experienced hot flashes and profuse perspiration. Since December, 1941, she has had a marked depression.

Urine analysis showed 10.7 and 12.2 micrograms of estrone in two 24-hour specimens. The values for the 17-ketosteroids were 10.0 and 8.2 mg.

On April 10, 1942, therapy with ethinyl estradiol, .05 mg. three times a day for 3 days followed by .05 mg. twice a day was instituted. The .05 mg. twice a day has been continued. The patient reports she has no hot flashes and that the mental symptoms have improved. What might be considered as a toxic reaction occurred when the patient had taken .75 mg. of ethinyl estradiol. She had become increasingly nervous and nauseated. The dosage was increased somewhat and the nausea was alleviated.

The results in this case are considered excellent.

#### DISCUSSION

Most of our patients have been treated over a period of months. One toxic reaction was noted. *Case 1* had what might be classed as mild toxic symptoms which disappeared on cessation of therapy but did not recur when ethinyl estradiol was resumed. *Case 2* had an urticarial reaction when only

25 mg of ethinyl estradiol was given in a 4 day period. However, diethylstilbestrol had produced the same symptoms. The results in case 3 demonstrate that ethinyl estradiol can effectively replace theelin therapy. One failure of response to therapy was noted (case 4). The report of case 5 demonstrates the advisability of reducing the dosage as soon as possible with the hope that therapy may be discontinued. The results in case 6 may demonstrate the possibility of error in concluding that a toxic reaction has been encountered, since continuing the medication in increased dosage alleviated the menopause symptoms and nausea disappeared.

During the period of time in which ethinyl estradiol has been used, no evidence of liver damage or blood dyscrasia has been observed. From our experience it is possible to conclude that ethinyl estradiol is an effective and safe drug to use in the treatment of menopausal symptoms if the patient's tolerance for and requirement of the drug are cautiously ascertained. It should be noted that individual requirements are relatively small for maintaining the patient free of menopausal symptoms and that toxic reactions seldom occur.

## SUMMARY

Results of treatment of 18 menopausal patients over a period of 21 months are presented. All patients were under treatment 2 months or more and one for 13 months. Only one patient exhibited what might be considered a toxic reaction to ethinyl estradiol, in that urticarial lesions occurred after taking a small amount of the drug. This patient had had the same reaction to diethylstilbestrol. One must carefully evaluate 'toxic reactions' before concluding that such reactions are not a functional manifestation of a neurotic type. Finally, relatively small doses of ethinyl estradiol are effective in alleviating symptoms of the menopause and with its use uniformly good results have been obtained.

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# Studies on Prostatic Cancer

## V. Excretion of 17-Ketosteroids, Estrogens and Gonadotropins before and after Castration<sup>1</sup>

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FOR THE PAST several years we have been investigating the subject of cancer of the prostate from the standpoint of its clinical, pathologic, enzymatic and hormonal aspects (1, 2, 3). Fully aware of the difficulties involved in the estimation of gonadal secretion by urinary sex hormone determinations, we undertook a study of urinary hormones in a series of patients with prostatic cancer, before and after castration, in the hope of clarifying secretion-excretion relations and to determine the following: a). Are there qualitative and quantitative alterations of urinary hormone excretion in the patient with prostatic cancer? b). What effect does castration have on these hormones and is this effect different from that found in the castrate without prostatic disease? c). Do extragonadal sources of these urinary hormones come into play following castration? d). Is there a relation between the excretory levels of the sex hormones and certain clinical phenomena observed in the castrate?

A review of the literature reveals much work dealing with the urinary excretion of hormones in benign hypertrophy of the prostate including that of Moore et al. (4) and Dingemanse and Laquer (5). However, only a few deal with the hormonal excretion of the patient with prostatic cancer. Dingemanse and Laquer (5) report three cases in which the urinary androgens and estrogens were studied, reporting levels of 14, 7 and 17 international comb growth units per 24 hours for androgen excretion, and 10, 20 and 50 international units of estrogen per 24 hours, respectively, in these three. Satterthwaite et al. in 1941 (6) reported a study of the urinary excretion of total 17-ketosteroids over a period of 6 months in 10 cases of prostatic cancer in which surgical castration was performed in the treatment of the disease. They reported an average close to 5 mg. per

24 hours, and a postcastrational decrease of from 12 to 60 per cent, presumably 6 months after castration. In their group of 10 patients, clinical improvement was correlated with the percentage decrease in the 17-ketosteroids.

With reference to the levels of urinary sex hormones in the castrate and the aging normal male, the authors wish to refer to the excellent works of Kenyon et al. (7), McCullagh (8) and Callow, Callow and Emmens (9); specific reference will be made to these results later in this paper.

### METHODS

*Collection, preservation and storage of urine samples.* In most instances, 24-hour collections of urine were obtained during the entire period of hospitalization which included a 6-day period before operation followed by a 7 to 21-day period after operation. Subsequent 24-hour collections were made at intervals varying from one week to one month subsequent to hospitalization.

Each sample was collected in a bottle, kept in the icebox and, with few exceptions, was extracted within 1 to 2 days. No preservative was used in this study except in a few recent collections when 10 cc. of concentrated HCl was added to the collection bottle. Results indicate that the only advantage of the initial acidification is to permit extraction to be done at a later date.

*Hydrolysis, extraction, purification and separation.* A few of the initial experiments were done using the Koch method of hydrolysis, extraction and separation (15 min. hydrolysis) (10). Subsequently, however, the method of hydrolysis and extraction of Consolazio and Talbot (11) was adopted; the method of separation described by Koch was retained. This method of hydrolysis and extraction was adopted because of the ease and constancy of steam-hydrolysis and the rapidity with which small volumes can be extracted. Briefly, the preliminary hydrolysis is carried out in an

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hydrolysis chamber employing steam at  $95^{\circ}\text{C}$  for a period of 20 minutes after acidification of 500 cc of fresh urine with 50 cc of concentrated  $\text{HCl}$ . The temperature of hydrolysis can be uniformly reached in 5 minutes from the icebox temperature. No sample is allowed to boil. Extraction is allowed to proceed for one hour in the Consolazio Talbot extractor which employs carbon tetrachloride circulating at a rate in excess of 3 liters per hour.

Following the extraction, the carbon tetrachloride is evaporated to dryness over a water bath and the residue taken up in ether. Separation into acid, neutral and phenolic fractions is made in the usual manner by shaking with saturated sodium bicarbonate, 10 per cent sodium hydroxide and 2N sulphuric acid. Decolorization with carbon was tried in a few recovery experiments but abandoned because of loss of active material. After this fractionation, the acid fraction is discarded. The neutral fraction is then evaporated to dryness, dried with absolute alcohol and ether and quantitatively transferred with absolute alcohol to volumetric flasks and later to storage bottles. This fraction is stored in the cold for further separation into *alpha* and *beta* fractions and for colorimetric assay. The phenolic fraction, after acidification with sulphuric acid and extraction with ether, is dried with absolute alcohol and quantitatively transferred through volumetric flasks to storage bottles, later it is taken up in sesame oil for bioassay of estrogens.

Further separations of a number of neutral extracts into ketonic and non ketonic fractions were made with Girard's reagent according to the method of Talbot, Butler and MacLachlan (12). Many of the neutral fractions and some of these ketonic extracts were separated into *alpha* and *beta* 17 ketosteroids by treatment with digitonin (13).

**Colorimetric assay.** The 17 ketosteroids were determined in the usual manner employing the Zimmerman reaction as modified by many (14, 15, 16). We adhered to the absolute alcohol technique and used the Evelyn colorimeter. We agree with Friedgood and Berman (16) that a reliable check of the method is had if double the intensity of color is obtained by doubling the amount of urine extract used for the assay. The above colorimetric procedure was also used to determine the *alpha* fraction and to obtain the *beta* ketosteroids by difference from the total. All results are expressed in terms of crystalline androsterone per 24 hours.

**Estrogen assay.** Aliquots of the phenolic fraction in alcohol, after quantitative transfer to suitable volumes of sesame oil, were assayed for their estrogen content.

for 3 successive days with 0.05 cc of the sesame oil solution of hormone. Six animals were used per sample, and 18 hours after the final injection, were killed and the uterus weighed on a torsion balance. At the time of each assay of a large number of specimens, determinations of the uterine weight response were made on 5 control animals injected with sesame oil alone and 3 groups of 5 mice each injected with pure diethylstilbestrol in sesame oil (0.005, 0.01 and 0.02  $\mu\text{g}$ ). The above authors, determining the relative activity of a number of estrogenic substances, found that the relative activity of diethylstilbestrol was 250 per cent when compared to estrone the activity of which was arbitrarily set at 100 per cent. Calculations were made expressing the estrogen output in terms of international units per day using their factor for relative activity and a value of 0.10  $\mu\text{g}$  of crystalline estrone per one international unit.

**Gonadotropin assay.** To determine the urinary gonadotropin levels in these patients, the method of extraction of McCullagh and Bowman (17) was used employing fractional alcoholic precipitation. We are satisfied that the authors' conclusion, that this method results in a quantitative, non toxic extract, is completely justified because rarely did an animal die as a result of toxic manifestations such as cutaneous ulceration. These animals were injected twice daily with 0.5 cc of the aqueous solution of the hormone for 3 successive days, the same kind of mouse being used as for the estrogen determinations. Six animals were used per extract, two mice received a 1:1 dilution of the 24 hour extract, two a 1:4 dilution and two a 1:16 dilution. The mice were killed 18 hours after the last injection and the uterus weighed.

No standard gonadotropic powder was available for quantitative expression of the results of these determinations. However, quantitative expression was made in terms of diethylstilbestrol equivalents. In parallel assays were made using diethylstilbestrol solutions as stimulators of uterine weight. In addition, an expression useful to us alone has been made using the percentage increase in uterine weight over that of un.injected controls.

## RESULTS

**Range of normal values for 17 ketosteroids.** The range of 17 ketosteroid excretion for 10 men between the ages of 20 and 40 was 11.6 to 17.5 mg per 24 hours with an average of 14.3 mg per 24 hours. Five women, ages 20 to 35, excreted from 5.6 to 15.5 mg per 24 hours with an average of 10.1 mg per 24 hours. These values are in close agreement with those of Albright et al. (19) who reported 13.8 mg per 24 hours for males and 9.0 mg per 24 hours for females, which were higher than the values for hospital patients given by Callow and associates (20) of 9.05

Koch (17). These animals were injected twice daily



mg. per day for males and 6.75 mg. per day for females. Our results indicate, as do those of others (21, 22), that before puberty the values are low (1.1 to 4.2 mg. per 24 hours). The lowest value was obtained in a 3-year-old boy, the highest in a boy age 12 years.

Having established normal values indicative of the reliability of the method, we studied two patients before and after operative procedures other than castration to determine the effect of an operative procedure *per se*. These two patients had hydrocelectomies under spinal anesthesia. Case 1 showed no

TABLE 1. 17-KETOSTEROID EXCRETION IN THE URINE OF A PATIENT BEFORE AND AFTER A HYDROCELECTOMY UNDER SPINAL ANESTHESIA

| Time Since Operation, days | Urine Volume, cc., 1 day | 17-Ketosteroid, mg., 1 day |
|----------------------------|--------------------------|----------------------------|
| 0                          | 670                      | 13.4                       |
| 1                          | 590                      | 12.9                       |
| 2                          | 750                      | 19.5                       |
| 3                          | 460                      | 10.3                       |
| 4                          | 2670                     | 24.0                       |
| 5                          | 1260                     | 11.6                       |
| 6                          | 1590                     | 13.7                       |
| 7                          | 810                      | 3.5                        |
| 8                          | 1700                     | 17.0                       |
| 15                         | 1680                     | 14.9                       |

change in the excretion of 17-ketosteroids for a period of 20 days postoperatively. Patient 2, table 1, showed no consistent change in 15 days. Of added interest is the fact that this patient had a temperature elevation of 101° F. on the third, fourth and fifth postoperative days. Further data, however, are necessary to determine any specific effect of trauma, anesthesia or fever on the output of urinary ketosteroids. We are cognizant of the opposite findings of Albright and

associates (19) and shall discuss later the effect of debility on urinary steroid output.

*Levels of urinary 17-ketosteroid excretion in prostatic cancer before and after castration.* The excretion of the 17-ketosteroids in 10 patients with prostatic cancer has been studied over a period ranging from 49 to 233 days, 140 individual urinary extractions having been made. In table 2 are shown the results. These values are for total 17-ketosteroids and do not include determinations to be shown for purified ketonic, and *alpha* and *beta* separations. These 10 patients are part of a series reported previously (1) upon whom multiple serum phosphatase determinations as well as roentgen-ray and other studies were made. All of these patients had roentgen-ray evidence of skeletal metastases at some period of their disease. The average value for the group for the 6-day period of observation before castration was 7.62 mg. per 24 hours with a range of 3.6 to 11.7 mg. per 24 hours.

After castration the level of total 17-ketosteroids fell in all cases. As indicated in table 2, the range of the lowest postoperative levels was from 0.4 to 7.4 mg. per 24 hours with an average of 3.49 mg. per 24 hours. This lowest level occurred from 2 to 14 days postoperatively in 9 cases and at 100 days in one case. The average time of the appearance of the lowest levels for the 10 patients was 15.8 days, but excluding patient G.T.R., the average time was 6.5 days. This fall was not sustained as reported by Satterthwaite et al. (6) but gradually rose in all but one patient (J.A.Y.) to a level higher than before castration, ranging from 7.3 to 24.4 mg. per 24 hours and averaging 11.4 mg. per 24 hours. A typical response to castration is graphically illustrated in figure 1 (Case 3, table 2).

TABLE 2. 17-KETOSTEROID EXCRETION IN THE URINE OF PATIENTS WITH PROSTATIC CANCER BEFORE AND AFTER CASTRATION

| Case No. | Subject | Age | Preoperative Average of 17-Ketosteroid, mg. per day | Lowest Post-Operative level of 17-Ketosteroid, mg. per day | Time Since Castration, days | Highest Postoperative Level of 17-Ketosteroid, mg. per day | Time Since Castration, days | Last Value of 17-Ketosteroid Observed, mg. per day | Total No. of Post-Operative Days Observed | Total No. of Urine Samples Extracted |
|----------|---------|-----|---|--|-----------------------------|--|-----------------------------|--|---|--------------------------------------|
| 1        | G.N.A.  | 53  | 3.6   | 0.4  | 3                           | 15.9   | 12                          | 9.4  | 49  | 8                                    |
| 2        | A.E.D.  | 58  | 5.7   | 3.8  | 14                          | 9.8  | 233                         | 9.8  | 233                                       | 16                                   |
| 3        | J.D.J.  | 58  | 7.3   | 5.0  | 10                          | 10.4   | 187                         | 10.4   | 187                                       | 15                                   |
| 4        | F.M.    | 47  | 10.8  | 5.3  | 3                           | 15.4   | 27                          | 11.1   | 183                                       | 8                                    |
| 5        | J.H.Q.  | 80  | 5.3   | 2.1  | 2                           | 7.3  | 86                          | 7.3  | 86  | 20                                   |
| 6        | G.T.R.  | 56  | 10.8  | 7.4  | 100                         | 19.3   | 4                           | 14.0   | 128                                       | 15                                   |
| 7        | J.T.    | 67  | 11.7  | 3.1  | 13                          | 12.3   | 67                          | 12.3   | 67  | 18                                   |
| 8        | J.J.T.  | 70  | 4.2   | 2.0  | 3                           | 10.2   | 115                         | 7.8  | 183                                       | 10                                   |
| 9        | W.W.    | 67  | 7.0   | 1.6  | 3                           | 31.4   | 175                         | 24.4   | 200                                       | 20                                   |
| 10       | J.A.Y.  | 71  | 9.8   | 4.2  | 7                           | 7.5  | 106                         | 7.5  | 106                                       | 10                                   |
| Average  |         | 63  | 7.62  | 3.49   | 15.8 (6.5) <sup>1</sup>     | 13.95  | 101.2                       | 11.4   | 142.2                                     | 14                                   |

<sup>1</sup> Average time since castration excluding G.T.R.

In addition to these 10 patients followed before and after castration, we wish to report the values for 10 patients who were castrated for prostatic cancer, but on whom no preoperative values were obtained. Table 3 shows a range of 1.8 to 16.24 mg per 24 hours with an average of 6.6 mg per 24 hours for

of the total with an average close to 10 per cent. Five patients showed a considerable fall in this fraction after castration, one a rise and one almost no change. Of the 5 showing a decrease, 4 were observed sufficiently long after castration for the postcastrational rise in total ketosteroids to become manifest. In the

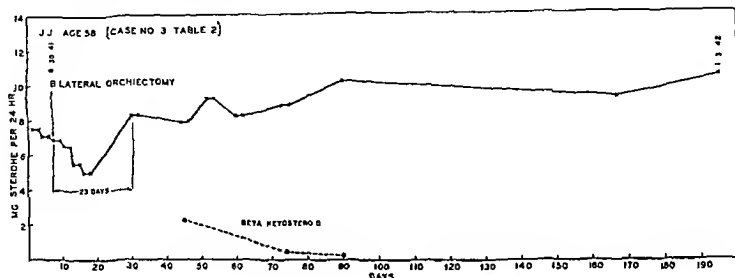


FIG 1

periods ranging from 7 to 23 months after castration.

**Colorimetric values for ketonic and non-ketonic fractions of the total 17 ketosteroids.** Separations into ketonic and non ketonic fractions with Girard's reagent t were made on 40 crude samples having a 17 ketosteroid value of 3.7 to 14.0 mg per 24 hours. At these levels, the range of the ketonic fraction was 89 to 96 per cent of the total (average 94 per cent). Unfortunately, no separations were made of such extreme values as 0.4 and 31.4 mg per 24 hours.

**Levels of alpha and beta ketosteroids before and after castration.** Thirty neutral extracts were separated into alpha and beta fractions. Table 4 lists 21 of the 30 values. The remaining separations were on the urine of castrates upon whom no preoperative studies were made. In these 7 patients,  $\beta$  ketosteroid excretion before operation ranged from 1 to 29 per cent

group without preoperative values, the level of the beta fraction never exceeded 8 per cent of the total.

**Urinary estrogen levels before and after castration.** Multiple determinations of urinary estrogens were made on 6 of the 10 patients described above, both before and after castration (table 5). Before castration

TABLE 4 URINARY BETA-KETOSTEROID BEFORE AND AFTER CASTRATION

| Case No | Subject | Age, yr | Time Since Castration, days | 17 Keto steroid, mg per day | Percent-age, beta |
|---------|---------|---------|-----------------------------|-----------------------------|-------------------|
| 2       | AED     | 58      | 0                           | 6.44                        | 11                |
|         |         |         | 23                          | 7.26                        | 5                 |
|         |         |         | 103                         | 7.92                        | 5                 |
| 3       | JDJ     | 58      | 42                          | 7.93                        | 29                |
|         |         |         | 70                          | 8.84                        | 4                 |
|         |         |         | 85                          | 10.2                        | 2                 |
| 5       | JHQ     | 80      | 0                           | 3.65                        | 11                |
|         |         |         | 5                           | 2.94                        | 11                |
|         |         |         | 17                          | 4.58                        | 3                 |
| 6       | GTR     | 56      | 0                           | 10.5                        | 0                 |
|         |         |         | 7                           | 13.7                        | 8                 |
|         |         |         | 22                          | 12.33                       | 0                 |
|         |         |         | 44                          | 13.8                        | 1                 |
| 8       | JJT     | 70      | 0                           | 5.33                        | 10                |
|         |         |         | 6                           | 4.5                         | 1                 |
|         |         |         | 26                          | 6.47                        | 2.5               |
| 9       | WW      | 67      | 0                           | 6.38                        | 2                 |
|         |         |         | 15                          | 7.4                         | 5                 |
| 10      | JAY     | 71      | 0                           | 8.58                        | 1                 |
|         |         |         | 14                          | 6.4                         | 11                |
|         |         |         | 21                          | 5.15                        | 2                 |

TABLE 3 17 KETOSTEROID EXCRETION IN THE URINE OF PATIENTS WITH PROSTATIC CANCER AFTER CASTRATION

| Case No | Subject | Age, yr | Time Since Castration months | 17 Keto-steroid mg per day |
|---------|---------|---------|------------------------------|----------------------------|
| 11      | AJ      | 75      | 23                           | 3.7                        |
| 12      | EFK     | 64      | 21                           | 6.9                        |
| 13      | MM      | 56      | 14                           | 9.14                       |
| 14      | AY      | 71      | 7                            | 5.4                        |
| 15      | CB      | 61      | 12                           | 16.24                      |
| 16      | JC      | 71      | 10                           | 3.9                        |
| 17      | PR      | 54      | 14                           | 9.15                       |
| 18      | GB      | 74      | 9                            | 2.8                        |
| 19      | GF      | 55      | 7                            | 1.8                        |
| 20      | EB      | 73      | 15                           | 6.9                        |
| Average |         | 65      | 13                           | 6.6                        |

the average excretion for the group was between 12 and 13 I.U. per 24 hours with a range of 1 to 24 I.U. per 24 hours. The last 4 patients illustrated show considerable lowering of the urinary estrogens at the end of the period of observation. Difficult to reconcile with these consistently low values are 3 single postoperative determinations on 3 patients upon whom no preoperative study of estrogen excretion was made. (Case 2, 9 and 10, table 2) Case 2, A.E.D., excreted 187 I.U. per 24 hours 2 months after castration. Case 9, W.W., excreted 110 I.U. per 24 hours 2 months after operation. Case 10, J.A.Y., two weeks after

hormone sufficient to produce from a 125 to 200 per cent increase in uterine weight when compared with the uninjected controls. Measured in diethylstilbestrol equivalents per day, this ranged from 0.55 to 0.65 µg. per 24 hours. After castration, at the end of the period of observation, all showed an increase in gonadotropic excretion. Although moderate, this increase ranged from 5 to 80 per cent, i.e. a 5 to 80 per cent increase in uterine weight above the increase observed preoperatively. The most striking rise was observed in a patient, age 63, with prostatic cancer who died of a pulmonary embolism 14 days after castration. Three days after castration, this man was excreting sufficient gonadotropic material in the urine to cause a 500 per cent increase in mouse uterine weight over the controls. Before operation, the value in this patient was 160 per cent.

TABLE 5 URINARY ESTROGENS BEFORE AND AFTER CASTRATION

| Case No | Subject | Age, yr. | Time Since Castration, days | Estrogen, I U per day |
|---------|---------|----------|-----------------------------|-----------------------|
| 1       | G.N.A.  | 53       | 0                           | 1 7                   |
|         |         |          | 26                          | 15 5                  |
| 4       | F.M.    | 47       | 0                           | 7 5                   |
|         |         |          | 27                          | 16 2                  |
|         |         |          | 41                          | 8 75                  |
| 5       | J.H.Q.  | 80       | 0                           | 23 75                 |
|         |         |          | 5                           | 4 75                  |
|         |         |          | 14                          | 2 5                   |
|         |         |          | 17                          | 1 62                  |
|         |         |          | 58                          | 2 1                   |
| 6       | G.T.R.  | 56       | 114                         | 6 0                   |
|         |         |          | 0                           | 18 7                  |
|         |         |          | 16                          | 0                     |
|         |         |          | 43                          | 9 0                   |
| 7       | J.T.    | 67       | 128                         | 5 8                   |
|         |         |          | 0                           | 8 5                   |
|         |         |          | 5                           | 3 25                  |
|         |         |          | 8                           | 1 75                  |
|         |         |          | 31                          | 3 75                  |
| 8       | J.J.T.  | 70       | 72                          | 3 5                   |
|         |         |          | 0                           | 12 5                  |
|         |         |          | 3                           | 3 25                  |
|         |         |          | 19                          | 8 0                   |
|         |         |          | 26                          | 4 2                   |
|         |         |          | 46                          | 15 0                  |
|         |         |          | 87                          | 11 5                  |
|         |         |          | 135                         | 2 6                   |

DISCUSSION

Our findings with reference to the quantity of 17-ketosteroid excreted by patients with prostatic cancer before castration indicate a), that the excretion of these substances is usually lower than in the normal male 20 to 40 years of age; b), that these patients excrete about the same amount of 17-ketosteroid as do normal males, age 60 to 70 years; c), that the values for these patients agree nicely with the value for castrates given by Callow et al. (20). These workers studied a series of 10 males, ages 19 to 46 years, who had been castrated 1 to 22 years before and found a 17-ketosteroid excretion ranging from 3.1 to 10.9 mg per day with an average of 7.8 mg. per day. Our pre-castrational average, as indicated in table 2, was 7.62 mg. per day.

Although the initial levels in our patients are low, there is a further decrease in excretion of these steroids after castration. Two factors may be responsible for this decrease a), removal of the testes may lead to a further reduction in urinary activity, b), operative trauma and anesthesia may be responsible for the lowering.

However, shortly after this initial fall in urinary steroids, a gradual, steady rise occurs to a level 50 per cent above the precastrational value. How long this secondary rise continues has not been determined. It would appear from the results on the 10 patients without preoperative values (table 3) that in 7 to 23 months the precastrational level is again approached, indicating a secondary fall in 17-ketosteroids. Further determination on the group on whom multiple determinations were made may fill in this gap.

The explanation of the postcastrational rise in 17-ketosteroids is difficult. Two factors may be responsible a), a deficiency in gonadal secretion may be compensated for by increased activity of the adrenals,

operation, excreted 78 I.U. per 24 hours. These three levels, all postoperative, were the only ones in the carcinoma group which exceeded 24 I.U. per 24 hours either before or after castration. Using the same method of extraction and assay, we found the range in normal females, ages 20 to 35 years, to be 90 to 150 I.U. per 24 hours.

Urinary gonadotropins before and after castration. Gonadotropic hormone was present in the urine of all men with carcinoma of the prostate. Three patients (Case 1, 5 and 7, table 2) were followed for 3, 4 and 5 months after castration. Preoperatively, quantities of gonadotropic

b), an improvement in the patient's general condition may lead to an increase in steroid production and excretion. This second factor would be accomplished by some organ such as the adrenal which ordinarily contributes a large part of the urinary steroids. Evidence to support the first factor, i.e. reciprocal relations of the adrenal cortex and testes, has been advanced by a number of workers including Hamblen et al (23) and Callow et al (20). Hamblen and associates, studying the 17 ketosteroids in the urine of women past the climacteric, concluded that an increased production of androgens by the adrenal compensates for regressive changes in the aging sexual system, or, in his words 'that the adrenal becomes the gonads of the aged'. Callow et al (20) thought that dehydroisoandrosterone might be identified as the characteristic excretory product of the adrenal cortex. If this were true, it would be possible to determine such a reciprocal relation of adrenal cortex and testes. They report one case in which the urine of a eunuch was found to contain an increased proportion of dehydroisoandrosterone over that in normal males. It will be noted that in our series, following castration, there was a consistent decrease in the *beta* fraction not an increase, indicating that the secondary 'compensatory' rise in 17 ketosteroids can not be explained on the basis of dehydroisoandrosterone and would indicate further that it is improbable that dehydroisoandrosterone is the characteristic excretory product of the adrenal cortex.

With reference to the qualitative nature of keto steroid excretion in prostatic cancer, we can only state that the *beta* fraction is about 10 per cent of the total, a figure which agrees nicely with that given by Talbot and Butler for the adult male (12). These investigators found that the average daily excretion of a ketosteroid paralleled the total output while values for the *beta* fraction were found to range from 8 to 15 per cent of the total. This, they indicated, was in close agreement with the value of 10 per cent *beta* found by Butenandt by actual chemical isolation.

Estrogen levels in the aging individual with prostatic cancer are low and there is a further decrease after castration, at least in the individuals on whom multiple preoperative and postoperative values were obtained. The high, single postcastrational values given are hard to evaluate unless here, as may be the case with the 17 ketosteroids, the adrenals compensate by increased activity when the testes are removed.

Urinary gonadotropins are low in these patients before castration. However, there is a moderate rise in gonadotropins after castration. This moderate increase would indicate that the testes are producing smaller amounts of androgen than in the younger male. Consequently, removal of the testes would lead

to less pituitary activity than if the androgen titer were high.

Three specific clinical observations are relevant in relation to the urinary hormonal status of these patients after castration: a), 'hot flashes' with or without sweating occurred in 8 of the 10 patients whose urinary hormonal excretion was extensively studied, b), estimation of the size of the prostate by digital examination through the rectum revealed a decrease in the size of the gland in 9 of the 10 patients, c), every patient lost his libido and 8 in 10 expressed an inability to have a penile erection within two months after castration. To date there has been no return of sexual powers. These phenomena have always been associated with what has been termed 'primary gonadal insufficiency'. Hamilton and Catchpole (24) have found this primary gonadal insufficiency to be associated with a decrease in gonadal secretions and an increase in the quantities of urinary gonadotropins.

It appears that primary gonadal insufficiency occurs after castration of the aging male with only moderate changes in urinary hormonal excretion. It may be that in the aging castrate minor changes such as we have observed are of as much significance as greater changes in the younger castrate. However, our results appear to substantiate the original conclusion of Brinzel (25) that a demonstration of sex hormones in the urine can not be regarded as evidence of the functional capacity of the gonads.

#### SUMMARY AND CONCLUSIONS

Urinary hormone levels are described for a series of patients with prostatic cancer both before and after castration.

Before castration, the level of 17 ketosteroids in a series of 10 patients averaged 7.62 mg. per 24 hours. This level is well below that for normal males of a younger age, but very close to levels reported for normal, aging males and a series of 10 castrates reported by Callow et al (20).  $\beta$  Ketosteroids represent approximately 10 per cent of the total 17 ketosteroid excreted.

Castration leads first to a fall in 17 ketosteroids followed by a rise. The duration of this rise has not been determined but probably does not exceed one year.  $\beta$  Ketosteroids do not account for this increase, because after castration, this fraction falls to a low level.

Before castration, estrogen excretion is low, averaging 12 to 13  $\mu$  per 24 hours. Castration leads to a decrease in estrogen excretion in 4 of the 6 patients studied. However, single high postcastrational values have been observed.

Castration leads to a moderate rise in urinary gonadotropins, a rise, however, which is slight compared to the values reported for younger castrates.

It appears that signs and symptoms of so-called 'primary gonadal insufficiency' occur with only moderate changes in the urinary excretion of the ketosteroids, estrogens and gonadotropins.

These observations tend to substantiate the original conclusion of Bringel (25) that a demonstration of the sex hormones in the urine cannot be regarded as evidence of the functional capacity of the gonads.

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# Simple Easy Bruisability: A Pseudo-Hemorrhagic Diathesis of Probable Endocrine Origin

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WHILE INVESTIGATING the bleeding tendency in approximately five hundred subjects (1-9), we have encountered a number of patients who bruise easily following slight trauma, yet do not have spontaneous purpura. Easy bruising has been the only symptom in some patients, while others have suffered from various unrelated diseases. We have been impressed by the frequent occurrence in the group of certain constitutional factors which appear to bear some relationship to the etiology of this condition, which may be designated 'simple easy bruisability.'

Easy bruising occurs predominantly in women. It may be present from early childhood and is commonly a lifelong affliction. The skin of patients presenting this complaint is usually fair, thin, and unduly sensitive to sunlight and chemical irritants. The bruises occur most frequently in the arms and legs, in areas readily accessible to trauma and the lesions are seldom larger than 3 to 4 cm in diameter. The patients usually present at least one bruise and in severe cases may have as many as 20 or 30. When the condition becomes pronounced the ecchymoses appear after such slight trauma that it is difficult to distinguish them from those seen in patients afflicted with spontaneous purpura. This is particularly true in the elderly patient. There are no other symptoms of hemorrhagic disorders, except infrequent attacks of epistaxis and, on occasion, gingival bleeding after brushing the teeth. There is no tendency to post operative hemorrhage from laparotomy wounds, but excessive bleeding may follow tonsillectomy or the extraction of teeth.

In patients suffering from simple easy bruisability, the basal metabolic rate is frequently low, but clinical evidence of overt thyroid insufficiency is seldom present. Rather, there are symptoms of what might be termed 'dysthyroidism,' i.e. irritability, mental anxiety, nervousness, fatigability, peripheral circulatory disturbances, abnormal distribution of body fat, bone and joint pains and the unusual combination

of physical sluggishness associated with mental hyper-irritability. Often the onset of easy bruising occurs following hysterectomy. There is a striking frequency of menorrhagia, and the tendency to bruise may be increased immediately preceding or during the menstrual period, and at the time of the menopause. The state of nutrition of these patients is generally good. There are no evidences of specific vitamin de-

TABLE I. NORMAL VALUES FOR HEMOSTATIC TESTS

| Test  | Mean    | $\sigma_s$ | Range <sup>1</sup> |
|---|---------|------------|--------------------|
| Bleeding time (Ivy) in minutes  | 3.2     | 1.4        | 0.4 to 6.0         |
| Coagulation time (modified Lee and White) in minutes                                  | 8.8     | 2.7        | 3.4 to 14.2        |
| Platelet count (Rees and Ecker) per cu mm   | 422,000 | 87,000     | 248,000 to 595,000 |
| Extracorporeal volume of clot in per cent (5, 6)                                      | 9.1     | 7.5        | 5.4 to 24.1        |
| Prothrombin concentration (Quick) in per cent   |         |            | 70 to 100          |
| Capillary permeability (Dalldorf), number of petechiae with 200 mm Hg vacuum pressure |         |            | 0 to 10            |

<sup>1</sup> The statistical method was used in setting up the limits of normality for the bleeding time, coagulation time, extracorporeal volume of the clot, and platelet count. One hundred normal subjects were studied. The limits of significance of the data were set at two standard deviations, which includes approximately 95 per cent of the observations. The mean is taken at the point of reference. All measures which were calculated were at least three times their sampling errors. The limits of normality for the prothrombin concentration and capillary permeability were arbitrarily set by direct observation. The statistical method was not used for these two tests.

observations

deficiencies. The renal and hepatic functions are usually normal, and arterial hypertension does not occur more frequently than in the general population.

Wintrobe et al (15) found a history of easy bruising in the families of some patients suffering from idiopathic thrombocytopenic purpura. We have elicited no family history of hemorrhagic disorders in patients suffering from simple easy bruisability. The

latter appears to be an inherited characteristic only in so far as it affects the members of the family who are of fair complexion, whose skins are of thin texture, and who tend to burn or freckle, rather than tan in the sunlight.

Because of recent developments in the technique of investigation of the bleeding tendency, it seemed advisable to subject patients suffering from simple easy bruisability to more careful study than has heretofore been possible (1-11). Normal values for the hemostatic tests employed are given in table 1. The

diseases of the liver, in malignant hypertension and nephritis, in aplastic, myelophthisic and pernicious anemia, and in the course of some diseases affecting the skin, such as Cushing's syndrome and the Ehlers-Danlos syndrome. In these diseases there is usually a constant abnormality in the results of the hemostatic tests in spite of the fact that the microscopic appearance of the skin is frequently normal. However, in Cushing's syndrome, histologic examination of the skin (12) may show a loss of tissue in the deeper layers of the corium which allows the larger vessels to be

TABLE 2. RESULTS OF HEMOSTATIC TESTS IN 23 PERSONS SUFFERING FROM SIMPLE EASY BRUIABILITY

| Case Number | Age | Sex | Duration         | Bleeding Time in Minutes | Coagulation Time in Minutes | Prothrombin Concentration, % | Extracorpuscular Volume of Clot, % | Platelet Count, per cu. mm. | Capillary Permeability, No. of Petechiae |
|-------------|-----|-----|------------------|--------------------------|-----------------------------|------------------------------|------------------------------------|-----------------------------|--|
| 1           | 23  | F   | Six months       | 9.0                      | 11.0                        | 90                           | 10                                 | 380,000                     | 0  |
| 2           | 42  | M   | Three years      | 3.5                      | 11.5                        | 95                           | 19                                 | 310,000                     | 50                                       |
| 3           | 42  | F   | Since childhood  | 6.5                      | 12.5                        | 85                           | 11                                 | 660,000                     | 0  |
| 4           | 35  | F   | Since childhood  | 3.0                      | 7.5                         | 100                          | 4                                  | 520,000                     | 6  |
| 5           | 52  | F   | Since childhood  | 3.0                      | 11.0                        | 90                           | 9                                  | 380,000                     | 1  |
| 6           | 50  | F   | Since childhood  | 3.0                      | 9.0                         | 100                          | 2                                  | 550,000                     | 1  |
| 7           | 34  | F   | Twenty years     | 3.5                      | 7.0                         | 100                          | 5                                  | 540,000                     | 1  |
| 8           | 28  | F   | Since childhood  | 16.5                     | 11.5                        | 90                           | 6                                  | 510,000                     | 0  |
| 9           | 70  | F   | Since childhood  | 4.0                      | 8.0                         | 70                           | -6                                 | 540,000                     | 6  |
| 10          | 35  | F   | Since childhood  | 3.0                      | 11.0                        | 85                           | 18                                 | 310,000                     | 5  |
| 11          | 18  | F   | Since childhood  | 8.5                      | 9.5                         | 90                           | 20                                 | 360,000                     | 8  |
| 12          | 42  | F   | Since childhood  | 3.5                      | 13.0                        | 90                           | 25                                 | 310,000                     | 0  |
| 13          | 33  | F   | Five years       | 2.0                      | 7.5                         | 100                          | 6                                  | 550,000                     | 5  |
| 14          | 27  | F   | Since childhood  | 5.5                      | 9.0                         | 100                          | 15                                 | 410,000                     | 4  |
| 15          | 28  | F   | Since childhood  | 3.0                      | 7.0                         | 100                          | 35                                 | 330,000                     | 0  |
| 16          | 31  | F   | Six months       | 7.5                      | 6.0                         | 95                           | -1                                 | 410,000                     | 4  |
| 17          | 55  | F   | Since childhood  | 4.0                      | 6.5                         | 100                          | 35                                 | 400,000                     | 18                                       |
| 18          | 53  | F   | Twenty-six years | 2.5                      | 6.0                         | 100                          | -4                                 | 380,000                     | 30                                       |
| 19          | 60  | F   | Since childhood  | 9.0                      | 8.5                         | 80                           | 38                                 | 370,000                     | 6  |
| 20          | 30  | F   | Since childhood  | 2.5                      | 9.0                         | 90                           | 10                                 | 380,000                     | 1  |
| 21          | 63  | F   | Thirty-three yr. | 4.0                      | 7.0                         | 80                           | 14                                 | 450,000                     | 0  |
| 22          | 40  | F   | Since childhood  | 2.5                      | 9.5                         | 100                          | 10                                 | 540,000                     | 0  |
| 23          | 42  | F   | Since childhood  | 5.0                      | 8.5                         | 90                           | 0                                  | 420,000                     | 0  |

results of the tests performed on patients suffering from simple easy bruisability are given in table 2. The most significant deviation from the normal was a slightly prolonged bleeding time which occurred in 6 of the 23 patients. The capillary permeability was increased in 3; and the clot retraction was diminished in 4. The coagulation time, prothrombin concentration and platelet counts were within normal limits. It is apparent that the factors responsible for this condition cannot be measured by the best available hemostatic tests. However, it seems probable that simple easy bruisability is caused by a combination of factors including undue thinness of the skin, abnormal fragility of the smaller blood vessels and defective cushioning of the subcutaneous vascular bed.

In addition to simple easy bruisability, ecchymoses may occur after slight trauma in various hemorrhagic diatheses such as thrombocytopenic purpura and hemophilia, in obstructive jaundice and

brought nearer to the surface. The capillaries may be increased in number and may show qualitative changes. Likewise, in the Ehlers-Danlos syndrome (13, 14), which is characterized by hyper-elasticity of the skin, hyper-extensibility of the joints and increased friability of the skin and its blood vessels, there may be found a relative absence of the fibrous trabeculae which normally bind the cutis to the deeper structures. We have studied biopsy specimens of skin removed from patients suffering from simple easy bruisability and are unable to report any significant alterations.

Easy bruising is likely to be considered of no significance when it occurs in persons who are otherwise in normal health. On the other hand, it may be confused with true purpura of more serious prognostic import when it is present in patients suffering from malignant hypertension or diseases of the spleen, liver, kidneys, or hematopoietic system. Furthermore,

the tendency to simple easy bruising may cause unwarranted hesitation to perform necessary surgical procedures. In addition, the ease with which bruises are sustained may be of some medico legal importance.

Many remedies have been tried in the treatment of simple easy bruisability. Small doses of desiccated thyroid substance have been of benefit in some cases. One patient who had suffered from easy bruisability for 5 years recovered after the use of  $\alpha$  estradiol. Nicotinic acid, cevitamic acid and vitamin K have proved to be of no value. The tendency to easy bruising disappeared spontaneously in one patient in whom the condition had been present for 6 months.

#### SUMMARY

Simple easy bruisability is found predominantly in women who are of fair complexion, have a thin textured skin, who present symptoms of endocrine dysfunction and frequently suffer from menstrual disorders. It is not due to any defect in the coagulability of the blood or decrease in the number of platelets. It is probably caused by a combination of factors, including undue thinness of the skin, abnormal fragility of the smaller blood vessels and defective cushioning of the subcutaneous vascular bed. Small doses of desiccated thyroid substance may be effective in the treatment of this condition.

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# A Personal Note on Methyl Testosterone in Hypogonadism<sup>1</sup>

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THIS ANONYMOUS REPORT by a eunuchoid physician is extraordinary. Since the data for many clinical experiments are obtained from patients who have no scientific training, this report is especially valuable because the observer is a physician trained in endocrinology. Although he does not wish to be identified, he deserves full credit.

Synthetic androgens offer a new horizon in the treatment of the adult eunuchoid syndrome. This is especially welcome to those patients who have received abundant pituitary preparations without discernible benefit. Many of the claims for the testosterone may have seemed too enthusiastic. While a healthy skepticism is commendable, adherence to this attitude in the face of clinical evidence to the contrary may deprive the eunuchoid patient of therapeutic benefits which will immeasurably add to his well being and happiness.

Testosterone propionate has been administered by injection (1, 2) and testosterone by subcutaneous implantation of pellets (3). More recently methyl testosterone, when given in sufficient amounts, has been found to be active orally (4, 5, 6). The therapeutic benefits of the oral form, when used in proper dosage, are as great as by injection or pellet implantation.

The majority of the reports on the use of testosterone deal chiefly with the more obvious effects on the external genitalia, while scant attention is paid to the effect of therapy on the patient as an individual. It is for this reason that a report of a successfully treated patient, who is a physician with considerable endocrine training, may be justified.

## CASE REPORT

This patient, 32 years old, 6 feet tall, weighed 178 pounds. Aside from the endocrine features, the physical

examination was essentially negative. The general appearance of the patient gave the impression he was at least 10 years younger than his true age of 32. The bodily configuration was typically eunuchoid. The pelvis was broad and feminine. The length of the extremities, especially the lower, was disproportionate to the trunk length. The musculature was poorly developed. The skin was smooth, pale, and devoid of hair except for the hair of the head and a few sparse pubic and axillary hairs.

The external genitalia were infantile. The penis, approximately 2.5 cm. in length, was nearly buried in the puberal fat. A small scrotum contained testes slightly larger than the common bean. They were relatively insensitive to pressure. No prostatic tissue could be palpated.

Routine blood and urine studies were negative. The basal metabolic rate had averaged between -15 and -22 per cent over a period of several years. Extraction of the urine for testicular hormone was consistently negative by a method that yielded an average of 20 bird units per liter in the normal male. Roentgenograms showed the major epiphyses ununited.

The patient had been treated extensively with various gonadotropic pituitary and pituitary-like preparations during the preceding 15 years. At one period he had received as much as 500 R.U. of anterior pituitary-like gonadotropic substance per day for 25 days. He had never shown the slightest response to any therapy.

In August, 1940, the patient was treated with 20 mg. of testosterone propionate in a cream base by inunction. The application usually was made before retiring. Successive regions on the trunk and extremities were utilized to facilitate absorption.

At the end of the first 48 hours the skin of the scrotum, nipples, and penis was noted to be hyperemic. By the fourth day penile erections occurred as frequently as once per hour. After treatment for one month the skin of the nipples and of the external genitalia, especially the scrotum, had become darkly pigmented. The scrotal skin had become redundant, thickened, and rugose. The penis had doubled in size, partly due to a constant semiturgid state. The testes, apparently not affected by the treatment, remained small. At the superior pole of each testis, a small, slightly tender mass was noted, possibly indicating some development of the epididymis. After about 30 days of treatment the patient experienced a seminal emission. The fluid was colorless and watery, and did not coagulate. The volume was estimated at 0.25 cc.

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<sup>1</sup> The liberal supplies of testosterone ointment (Oreton-F) and methyl testosterone (Oreton-M) used in this study were furnished by Dr. W. H. Stoner of the Schering Corporation, Bloomfield, N. J.

Microscopically the fluid was noted to be composed of mucus and to contain many polymorphonuclear leukocytes

The few pubic hairs present grew rapidly and many new hair follicles developed. The previous hair was brown, soft, silky, and straight. The new hair was jet black, coarse, and curly. The distribution of the new follicles was feminine. No effect was noted on the hair of the axilla, head or face.

Testosterone ointment produced a general feeling of well being, but sexual drive was lacking. It occurred subsequently with the use of methyl testosterone. There was no especial change in muscular energy or endurance. Careful checks showed no variation in body weight.

During the entire period of treatment by injection,

regressed to approximately the state before the use of androgens. The pigmentation, especially of the nipples and the scrotum, faded considerably. Erections did not occur. There was some diminution of the feeling of general well being.

Initial treatment with methyl testosterone was begun in November. During the first week the dosage was low in order to avoid possible deleterious effects, but none was noted. No unusual effects were noted at a daily dose of below 20 mg. When the dose was raised to 40 mg there was a prompt occurrence of erections.

During the month of November an average of 40 mg of methyl testosterone a day was taken orally. This level seemed to produce effects similar to 20 mg of the testosterone ointment. It was noted early that the erections



Fig 1 August, 1940 Fig 2 February, 1941 Photographs approximately one half actual size

there was neither the slightest suggestion of skin irritation nor other contraindication to its continued use. There may have been slight urinary frequency.

After about 10 days of treatment, when it was apparent that the therapy was very effective, a photograph of the external genitalia was made. Except for a slightly increased growth of the pubic hair, the basic state before treatment was retained (fig 1). It will be noted that the genitalia are infantile and correspond to those of a preadolescent boy of under 10 years of age.

During the next 6 weeks (September and October) treatment was sporadic. Several days without treatment resulted in a prompt regression of the turgidity of the genitalia and fewer erections. It was astonishing to observe how promptly the regressive changes appeared when therapy was discontinued.

Methyl testosterone therapy became available during the latter part of October. In order that the effects of the oral preparation would not be confused with the previous therapy, treatment was omitted for a period of about 2 weeks. During this period the size of the external genitalia

were rather sharply conditioned by the size of the dose. This correlation was less obvious later in the treatment. Erections, an early sign, were nearly always noted within 12 to 36 hours after the ingestion of the tablets. The patient had a number of seminal emissions during the latter part of the month. Pubic hair and penile growth were rapidly increased. At this period the voice was first noted to assume a slightly hoarse quality. The patient became aware of a slight psychological change.

The external genitalia progressed as they had with injections. Increased pigmentation gradually darkened the skin, especially in the face. The patient had always appeared 'pale,' even when in a state of good health. The pigmentation took place in the winter months when there was almost no sunshine. It was noted by friends who were not aware of the treatment.

The sebaceous glands at the base of the nose became active, giving the nose an oily appearance. This had never been noted before. No change in the function of the sweat glands was observed.

In December, the average dose was raised to 60 mg

per day, whereupon considerable psychological change occurred. Libido was more marked. The voice had a definite huskiness and was slightly lower in pitch. A striking effect was the breaking of the pitch of the voice as in the adolescent boy. During this month the external genitalia increased in size but not as rapidly as was previously observed. The testes decreased slightly, were softer and less sensitive to pressure. This was not considered by the patient to contraindicate continuing treatment. He was delighted with the results of the treatment and felt better than he had in years.

In January, 1941, the average daily dose was raised to 80 mg. During this month there was a sharp drop in response to the medication. Libido decreased abruptly; the penis became less turgid than usual; the number of erections diminished. The voice continued to be husky. This regression is not readily explained. The observations made during this period served to prove the patient's reaction was not conditioned by his knowledge of the dose.

No therapy was taken for 10 days early in February. When resumed, a daily dose of 50 mg. was taken. The response was reasonably prompt but did not reach a great height. Almost no treatment was taken in the month of March. It was felt that a rest might prove beneficial. An average of about 10 mg. a day was taken during this period. Regression was quite prompt.

Treatment was resumed in April with an average daily dose of approximately 50 mg. By midsummer it was noted that the therapy was less effective. No treatment was taken for a month. When resumed the effect was slight. There had been relatively little increase in the size of the external genitalia, no marked change in hair growth, definitely diminished libido, and frequent seminal emissions. It seemed that while maintenance of the secondary sexual characteristics was achieved through treatment, there had been relatively small progress since mid-spring. Accordingly, as an experiment to determine the effect of increased dosage, 150 mg. (15 tablets) were given at one time, in the evening before retiring. By the end of 12 hours the external genitalia were turgid; it was noted that a full bladder produced priapism. At the end of 24 hours the penis was in a state of semi-erection constantly. Tingling was noted in the nipple. A mammary areola of approximately 3 cm. diameter could be palpated. The nipples were prominent, as is often observed in the adolescent boy. Libido was quite marked. Forty-eight hours after the ingestion of the 15 tablets these symptoms had all disappeared except that the breast tissue continued to be tender for several days. At the end of 72 hours the external genitalia resumed their former appearance except for a slight hyperemia. The patient has repeated the dosage of 150 mg. several times with identical results. Toxic effects have never been noted. No gastrointestinal intolerance has ever been observed. The only effect noted was a very slight increase in the frequency of urination. Nocturia was never reported by the patient.

### *Psychological Aspects of the Treatment*

Much of the value of this report will be found in the effect of the treatment on the mental state and

social activities of the patient. It is quite remarkable that a few tablets, taken daily, could so change the behavior and outlook of an individual.

In order better to appreciate the effects of androgenic therapy there must be some degree of insight into the patient's reactions before treatment.

Prior to therapy the patient had only the mildest interest in the opposite sex. He enjoyed a certain amount of social activity and had occasional 'dates,' but only to secure a partner for some social function. He was able to recall about 5 dates in the year before treatment. Contact with the opposite sex was in no way stimulating. The patient rarely indulged in the so-called 'necking' because he felt embarrassed. The patient had never had a seminal emission.

The general behavior of the patient was shy. He frequently over-compensated to the opposite extreme and appeared an unmitigated 'smart aleck.' He felt embarrassed in the presence of strangers because of his high-pitched voice, lack of beard, unmasculine contour, and youthful appearance. No doubt the patient was unduly sensitive regarding these points, but long years of being called 'Madam' over the telephone had sensitized him.

On the whole, the effects of testosterone were stimulation of rapid development of adolescence. The physical and psychological development which normally spreads over a period of years now took place in a few months. In the early part of the experiment, during the use of ointment, libido was very slight, although the physical stimulation was very evident. After the institution of the methyl testosterone libido became a prominent feature. This gradually increased as the treatment progressed; however, the stimulation was never uncontrollable. It should really be considered as a gentle, but nevertheless definite urge, rather than a true drive. Huskiness of the voice has progressed until now the normal speaking tone is much lower. He no longer is subject to telephone difficulties. Friends frequently notice the change and ask whether he has an upper respiratory infection. This single change as a result of the therapy is the most gratifying to the patient of all the responses.

The increased desire for feminine companionship, not based solely on sexual premises, resulted in an almost unbroken succession of 'dates.' The patient came to enjoy 'necking'; close contact frequently resulted in erections and seminal emissions.

Close friends of the patient remarked that the patient seemed 'more mature' and 'emotionally more stable.' He lost a great deal of his shyness, especially with the opposite sex.

The patient was subject to rather severe attacks of depression prior to therapy. These attacks usually

appeared without any known cause and very frequently extended over a period of several days. Since the institution of treatment the depressive attacks have practically ceased and there has been a definite improvement in his general spirits. The patient is definitely more aggressive.

The patient is emphatic in his declaration that the therapy has increased his general feeling of well being, and yet he is unable to give a logical explanation. He appears to make every attempt to be objective in his observations. He reports that when under treatment he definitely felt more pugnacious and was frequently surprised to find himself 'talking back to taxi drivers, and other things I wouldn't have done 6 months ago.'

#### RESULTS OF THE TREATMENT

The skin is more heavily pigmented, most pronounced in the external genitalia and the nipples. The sebaceous glands are much more active. The increased pigment has resulted in the loss of the patient's chronic 'pasty' appearance. The skin tans more easily when exposed to sunlight, but there has been no change in its general texture. There was no acne.

He doubts if there was any change in his energy output and states he felt just as tired after a difficult day in the hospital as before the institution of androgenic therapy.

The pubic hair was markedly affected by the therapy (fig. 2). Before treatment the pubic hair was limited to a few fine strands, after treatment it enveloped the entire pubis and scrotum and tended to be rather coarse, black, and recently slightly curly. There has been no typical masculine extension toward the umbilicus. However, recently there has been some suggestion that this may occur with further medication. Curiously enough, there was no effect on the axillary hair or hair of the head.

Only very recently (September, 1941) has there been evidence of development of a beard. The lanugo of the upper lip has become heavier and coarser. This is considered to be a promise of eventual development of a beard with further treatment. No change was noted in the hair of the extremities.

There has been no gain in weight as reported by some investigators (3, 7). The patient made careful observations regarding this point, weighing himself daily on the same hospital scale over a period of many months.

The size of the penis has been increased about three fold but the size of the testes has remained stationary. The epididymides, which before treatment were not palpable, have attained a size approximating that of the atrophic testes. The prostate was

not palpable prior to therapy. Very recently the prostate was palpated by a urologist who declared the gland to have two well developed lobes with a median furrow, and while small, to be within normal limits. The seminal fluid is normal microscopically except for a total absence of spermatozoa. The ejaculate has increased in volume from a few drops to about 2.5 cc. It is turbid and coagulates on standing.

The major epiphyses are ununited. Fluoroscopically no change has resulted from treatment.

Treatment resulted in a fairly marked lowering of the vocal pitch, noted by both the patient and friends. Recently there has been considerable increase in the size of the laryngeal prominence.

#### DISCUSSION

In this report, which is unique because the patient is also a physician, and functions as such, there are certain aspects of hypogonadal treatment which deserve consideration. The chief cause of concern to the hypogonadal individual is not his lack of sexual interest or ability, for indeed, how can he be concerned about a force of which he knows nothing? The lack of insight into this aspect is the principal mistake made by the average physician in the treatment of the eunuchoidal individual. Of far more concern to the patient are the distinct social handicaps of an effeminate appearance and the high pitched voice. Thus, while this report deals largely with the more obvious effects of the treatment, the sexual changes, I desire to stress that this phase represents only one link in the chain. So far as the patient is concerned, it is of less importance. Of far greater importance is the rehabilitation of the eunuchoidal patient into feeling that he is able to assume his place in the world as a normal person.

Oral therapy appears to be the choice in adult hypogonadism. Implantation of pellets has many basic difficulties and the dosage is not amenable to regulation (7).

Increased tolerance has been noted by others (4). In the case reported, the tolerance developed over a period of 6 months to the point where a daily dose of 100 mg. was required to produce the response originally noted at 40 mg. Interruption of treatment over a period of several weeks appeared to restore partial sensitivity to the hormone. The sole deleterious effect was the production of a mild gynecomastia which occurred only with larger doses (8).

#### SUMMARY

1. Oral therapy by methyl testosterone is capable of initiating normal adolescent changes in an adult eunuchoid individual.

2. No toxic effects resulted from massive doses of the synthetic hormone.
3. There is a suggestion that a tolerance to the substance may be developed.
4. Methyl testosterone appears to be the product of choice in treatment of the adult hypogonadal individual.

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# Hypothyroidism, Hyperlipemia and Carotenemia

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THE RECOGNITION of the clinical picture of carotenemia is relatively new. In 1904 van Norden described this orange yellow pigmentation of selected areas of the skin in diabetics and called this disease xanthosis diabetica. That carotenemia was associated with some metabolic disturbance was suggested by van Norden's (1) publication in 1907, and, as further studies appeared in the literature, the correctness of this assumption became more apparent.

In 1919, Hess and Myers (2) described this same peculiar pigmentation of the skin occurring in children and called it carotenemia. They noted that this coloring appeared in two children who had ingested large amounts of lipochrome vegetables, but they were unable to reproduce this condition by the overfeeding of these same vegetables in control cases. Head and Johnson (3), reported the same phenomenon in malnourished children who were deprived of meat but had eaten an excess of pigment containing vegetables. The carotenemia subsided when this excess of lipochrome was removed from the diet. They were aware that this condition was not universal and that children exposed to the same dietary limitations and excesses did not all develop carotenemia. Stoner (4), in 1928, made the same observation and stated that carotenemia appeared uncommonly in adults and that its occurrence in children is associated with an increased vegetable intake.

Boeck and Yater (5), reporting the occurrence of xanthosis and xanthemia in variously diseased patients, showed that 86 per cent of the diabetics examined had xanthemia and that 100 per cent (of 22 cases) of those who had renal disease were xanthemic. Only 69 per cent of the patients with hepatic disease had xanthemia. In analyzing the cases of 36 patients with xanthemia, it was found that 10 were diabetics, 12 had "stomach trouble," 2 were jaundiced and the remaining 12 had indifferent or unrelated complaints.

The metabolism of carotene has been shown to take place in the liver (6, 7, 8), and one could expect an alteration of the blood carotene balance associated

with hepatic insufficiency. This, however, has not been demonstrated consistently, perhaps because of the lack of sensitivity of the various laboratory tests for liver function, or because complete studies were not made in all instances. When there is a demonstrable carotene imbalance there is always an associated, but not necessarily proportionate, change in blood lipid mobilization (9-12). What exact mechanism in liver function is altered in carotenemia is not known, but the most plausible explanation is that the liver is incapable of converting carotene to vitamin A (11, 12, 13), possibly because of the absence of carotenase. This results in an excess of carotene over and above the ability of the liver to store the lipochrome and, therefore, the blood serum is flooded with this excess. It accounts for the fact that clinical carotenemia is impossible to reproduce experimentally in normal controls (12).

The association of carotenemia and thyroid dysfunction is not unknown (13-17), and it has been shown that this relationship can be demonstrated *in vitro* (15). That this relationship should exist is not strange. Carotene is a lipochrome and it is natural to expect that a syndrome which affects the metabolism of lipochromes would also affect the mobilization of other lipoids whether they have a pigment base or not.

Euler and Klusman in 1932 (16) showed that white rats fed with large doses of carotene and thyroxine lost no weight, and Wendt (14) confirmed this antagonism of carotene and thyroxine by successfully decreasing the basal metabolic rate of hyperthyroid individuals by the feeding of large doses of a vitamin A preparation. The increased creatinine metabolism of hyperthyroid individuals was shown to be lessened by the administration of carotene (18, 19). Abelin (15) demonstrated that guinea pigs depleted of vitamin A and carotene, showed an absence of these substances in the liver, when the animals were fed carotene both of these substances reappeared in the liver, but if the diet were supplemented with both carotene and thyroxine instead of carotene alone, then the liver failed to show any storage of either carotene or vitamin A.

Experiments in vitro, (15), in which a mixture of carotene and thyroxin was allowed to incubate, showed that there is a progressive diminution in the quantity of both of these compounds.

In 1938, Anderson and Soley (20) reported 13 cases of carotenemia of whom 5 were hypothyroid; 3 cases showed evidence of hepatic damage, and one case had both hepatic insufficiency and hypothyroidism. Savy, Vachon and Vincent (21) reported 6 cases of carotenemia, 5 of whom had some hepatic dis-

TABLE 1. RESULTS OF LABORATORY TESTS PRIOR TO AND DURING THERAPY

| Test                        | Before Therapy | One Month of Therapy <sup>1</sup> | Two Months of Therapy <sup>1</sup> | Eight Months of Therapy <sup>1</sup> |
|-----------------------------|----------------|-----------------------------------|------------------------------------|--------------------------------------|
| Hemoglobin, %               | 70             | 81                                |                                    | 85                                   |
| Red blood cells, M./cu.mm.  | 3.35           | 3.55                              |                                    | 4.35                                 |
| Color index                 | 1.05           | 1.10                              |                                    | .98                                  |
| Total protein, gm. %        | 7.6            |                                   |                                    | 7.49                                 |
| Albumin, gm. %              | 5.2            |                                   |                                    | 4.77                                 |
| Globulin, mg. %             | 2.4            |                                   |                                    | 2.72                                 |
| Albumin/globulin ratio      | 2.17           |                                   |                                    | 1.75                                 |
| Nonprotein nitrogen, mg. %  | 33.8           |                                   |                                    | 36.0                                 |
| Total lipids, mg. %         | 1290.0         | 994.0                             |                                    | 597.0                                |
| Phospholipids, mg. %        | 252.5          |                                   |                                    |                                      |
| Lipid phosphorus, mg. %     | 10.1           |                                   |                                    |                                      |
| Cholesterol, mg. %          | 628.0          | 329                               | 201                                | 265.0                                |
| Free cholesterol, mg. %     | 142.0          | 87                                | 53.3                               | 61.4                                 |
| Percentage free cholesterol | 23             | 23                                | 26                                 | 23                                   |
| Icterus index               | 15.1           | 13.3                              |                                    |                                      |
| Carotenoids, mg. %          | 0.448          | 0.368                             | 0.220                              | 0.266 <sup>2</sup>                   |
| Basal metabolic rate, %     | -20            | -5                                | +9                                 | +1                                   |
| Body weight, lb.            | 157            | 149.5                             |                                    | 137                                  |

<sup>1</sup> Therapy was continuous throughout the 8-month period and consisted of ferrous sulfate, grains 15, per day and thyroid (whole gland), grains 6, per day.  
<sup>2</sup> Average normal blood carotene is 0.109 mg. per cent with a range from 0.054 to 0.176 (10).

turbance, and the other case, reported in detail elsewhere (13), was one of carotenemia associated with hypothyroidism. In a recent paper by Escamilla (22), 7 consecutive cases of hypothyroidism were presented, each having increased carotene pigments in the blood serum. Four cases were treated with thyroid, in 3 of which there was a consequent decrease in the blood carotene levels. His explanation for the carotenemia was a depression of liver function due to a lowered metabolism.

The case to be reported in this paper is similar to those described by Anderson and Soley (20) and Savy et al. (21). The case, however, presents a more detailed study of the blood lipid and metabolic changes, both during the course of the disease and following treatment.

CASE REPORT

M.S., a 36-year-old white male, entered the out-patient

department of the Jewish Hospital, on Jan. 28, 1941, complaining of weakness, fatigue and moderate exertional dyspnea of 2.5 years in duration. He stated that there was a change in his physical status about 4 years ago. At that time, he noted that his skin became coarser, that his scalp showed evidence of scaling, that he was losing his hair, not only on his head, but also on his chest and legs, and that there was some brittleness of his nails. He also complained of marked chilliness, constipation and loss of memory. In addition, the patient was on a thoroughly inadequate diet. Because of the appearance of pallor, an increase in weakness, fatigue and dyspnea, he finally consulted a physician in June, 1939. At that time he also noted vague paresthesias of the upper extremities. His local physician told him he had 'pernicious anemia' and prescribed liver, iron, yeast and various vitamin preparations. The blood picture showed an anemia, color index above 1 and a slight macrocytosis. The patient was advised as to diet and he began to consume large quantities of green vegetables in the form of carrot juice, celery and parsley. About 2 months after he started this diet, he noticed a gradual and progressive increase of yellowish discoloration in the skin, most marked on the palmar surfaces of the hands. However, despite the fact that the patient was getting adequate amounts of liver and iron, there was only slight improvement in the objective findings with the exception of some gain in weight and practically no subjective changes.

Physical examination at this time revealed a well-nourished, moderately obese male weighing 157 pounds (height 63.5 inches). There was a definite canary yellow color of the skin of the palms of the hands and the soles of the feet. There was also some slight pigmentation at the naso-labial folds. There was no evidence of skin pigmentation elsewhere. The face was puffy and sallow. Hair over the body was sparse and was absent on the thorax and legs. The finger nails were brittle. The tongue was clean and there was no evidence of glossitis or atrophy. The lungs were clear and the heart sounds were normal. Pulse rate was 62 per minute and the blood pressure was 118/80 mm Hg. The findings in the abdomen were negative, and the liver and spleen were not palpable. The genitalia were normal. Neurological examination revealed nothing abnormal; position and vibratory senses, as well as the deep reflexes, were intact.

Laboratory studies showed the following: red blood count, 3.35 M.cu.mm.; hemoglobin, 70 per cent; color index, 1.05. Urine had a specific gravity ranging from 10.10 to 10.20 with negative albumin and sugar and no formed elements. Electrocardiogram showed low voltage. Roentgen-ray study showed the chest was normal. In the first sample of the gastric extraction there were 86 units of free HCl and 100.6 units of total HCl. Galactose tolerance was normal. There was some increased tolerance for dextrose as shown by the glucose tolerance test. Bone marrow studies revealed no evidence of pernicious anemia or other blood dyscrasia. The basal metabolic rate was -20 per cent. The original blood lipid findings along with other determinations are given in table 1.

In view of the appearance of the patient and the low metabolic rate, the diagnosis of hypothyroidism was made.

In addition, subsidiary diagnoses were made of carotenemia and secondary anemia. Treatment was started on Feb. 13, 1941, with the administration of thyroid (whole gland) and iron. The patient's course was followed until October, 1941, at which time a final set of blood studies was made. The results of these tests, as well as those made on earlier occasions, are recorded in table 1.

Clinically, the improvement was remarkable. The slow, puffy appearance of the face disappeared. He appeared bright and alert. There was complete disappearance of the yellowish pigmentation of the palms and soles. The nails were no longer brittle. Hair began to appear on the chest and legs. There was also an increase in the amount of scalp hair. The anemia, which had failed to respond previously to both iron and liver therapy, was now controlled. There was a weight loss of 20 pounds and the basal metabolic rate was  $+1$  per cent. Subjectively, the improvement was also striking, fatigue, weakness and dyspnea had completely disappeared and the patient had no complaints.

#### COMMENT

Hyperlipemia usually occurs in various forms of anemia, including pernicious anemia, hemolytic anemia and leukemia, in diabetes mellitus, nephrosis and glomerulo-nephritis, biliary disease and hypothyroidism. Laboratory tests indicated only the presence of hypothyroidism. Clinically, too, the patient represented unquestionably a case of marked hypothyroidism. The basal metabolic rate was  $-20$  per cent, but still more important was the extremely high blood cholesterol. Concentration of this has been considered a more reliable index of the severity of hypothyroidism than the basal metabolic rate.

It is quite apparent that the patient had been ill for several years with hypothyroidism. In thyroid deficiency the pallor due to subcutaneous myxedema often is suggestive of severe anemia, which is not corroborated by the blood count. However, a moderate degree of anemia is not uncommon. Liver and iron are ineffective in the relief of the anemia unless administered with thyroid.

Carotene, or provitamin, is converted into vitamin A in the liver, where it is stored. The conversion is relatively slow and not complete, probably not more than 20 per cent of the ingested carotene is converted into the vitamin. Carotenemia is usually found in diseases exhibiting hyperlipemia, as diabetes mellitus, chronic nephritis, biliary disease and hypothyroidism. Carotene inactivates the action of thyroxine and this has been demonstrated clinically and experi-

mentally. It then suggests the hypothesis that patients with carotenemia may exhibit a symptom complex with clinical evidence of hypothyroidism and hepatic insufficiency. In this instance, however, hypothyroid symptoms were manifested for several years before the large intake of vegetable juices. Since carotene is fat soluble and there was a marked hyperlipemia, it is highly probable that the carotene was held in solution in high concentration and could not be adequately destroyed or removed by a presumably normally functioning liver.

The administration of large doses of thyroid resulted in a marked diminution of the blood lipids and carotinoids and an increase in the metabolic rate from  $-20$  to  $+1$  per cent. As the result of the administration of thyroid with iron, the anemia improved considerably.

#### CONCLUSION

A case is presented of hypothyroidism associated with hyperlipemia, carotenemia and anemia, which responded remarkably to thyroid and iron medication.

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# Synergism Between Pituitary Extracts and Chorionic Gonadotropins

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THE THERAPEUTIC ATTEMPTS to utilize gonadotropins for the correction of menstrual disorders have not proved to be quite satisfactory. Clinical ineffectiveness in a considerable percentage of the patients, on the one hand, and the danger of ovarian impairment, cystic or atretic changes, on the other, have not increased the popularity of gonadotropic therapy. Empirical clinical observations, however, have shown that the effectiveness of chorionic gonadotropins is augmented by simultaneous administration of pituitary extracts (1, 2). Thus it is possible to reduce the dosage of chorionic gonadotropin and minimize the undesirable alterations of the ovarian tissues.

The synergism between anterior lobe extracts and the chorionic factor was experimentally demonstrated by Evans et al. (3), Fevold et al. (4) and others. The increase in the effectiveness of the chorionic gonadotropin, according to the prevalent belief, is brought about by the pituitary gonadotropins, although the exclusive rôle of the latter in the process of synergism was questioned repeatedly. In a previous paper, we attempted to show that a pituitary extract of low gonadotropic potency is capable of producing significant weight increase and histological changes in ovaries and uteri; comparable effects were obtained also by utilizing Collip's specific metabolic principle as a synergist. A combination of minimal doses of the specific metabolic principle and of chorionic gonadotropin, each of which, when given alone was ineffective, increased ovarian weights 300 per cent and uterine weights 900 per cent.

By slightly increasing the amount of the chorionic factor and continuing its use for 10 days, even greater reactions were obtained; these equalled those described by Mazer and Ravetz (5) in their experiments on the synergistic effect of pituitary gonadotropins. Rats killed on the eleventh day showed an increase in the average for body weight from 36.5 to 70.5 gm. The ovarian weight averaged 47.5 mg. nearly 4 times

that of the controls, while the uterine weight was an average of 340 mg., nearly a 23-fold increase. Using a commercial preparation which is a combination of chorionic gonadotropin and gonadotropic hormone extracted from the anterior pituitary gland<sup>1</sup> and injecting one 'synergy' unit, ovarian weights of 50.5 mg. were obtained, yet the weight of the uteri increased to an average of only 68.5 mg.

Microscopically, the ovaries of the animals receiving the combination of the specific metabolic principle of Collip and the chorionic gonadotropin showed transformation of numerous follicles into lutein bodies while other follicles showed moderate cystic enlargement.

## EXPERIMENTAL PROCEDURE

Further studies were made to identify other pituitary factors present in the unfractionated extract which might produce synergistic effects. We used adrenotropic and thyrotropic extracts, a lactogenic preparation and a mixture of anterior pituitary factors assayed to contain 25 growth units per cc.<sup>2</sup> One unit of the adrenotropic factor was given as a total dose, divided into 6 injections and distributed over a period of 3 days. The animals were killed 96 hours after receiving the first injection. In a second series, chorionic gonadotropin<sup>3</sup> was added to the injection material for the total amount of 0.625 units per animal.

In the next experiment, thyrotropin was given for a total dose of 1.25 units, while a similar number of animals received, in addition, 0.625 units of chorionic gonadotropin.

A third group was given lactogenic hormone, 5 units as a total dose, while an equal number of animals received an added 0.625 units of chorionic gonadotropin.

<sup>1</sup> This preparation (Synapoidin) was supplied by Parke, Davis & Co., Detroit, Mich.

<sup>2</sup> We are indebted to Dr. F. Fenger of Armour & Co., Chicago Ill., for the various pituitary extracts used in these experiments.

<sup>3</sup> The chorionic gonadotropin (A.P.L.) was supplied by Ayerst McKenna & Harrison, Rouses Point, New York.

The next group received the mixture of anterior pituitary factors including growth hormone in a solution containing a total dose of one growth unit per animal while the same number of animals received an added 0.625 units of chorionic gonadotropin.

In another experiment, we combined adrenotropin and lactogenic hormone, one unit of the former and 5 of the latter, alone and with added chorionic gonadotropin.

In another experiment, the same mixture of adrenotropin and lactogenic hormone was used with the

ever, one or two lutein bodies were found in each ovary, some fairly well developed, others in the incipient stage of luteinization.

The marked increase in uterine weight obtained by combining these pituitary factors with chorionic gonadotropin, seems peculiar in view of the absence of commensurate ovarian enlargement such as was noticed before with the use of the unfractionated pituitary extract or the specific metabolic principle. We must assume, nevertheless, that these immature ovaries obtained sufficient stimulation to produce the

TABLE I. STUDY OF SYNERGISM BETWEEN PITUITARY EXTRACTS AND CHORIONIC GONADOTROPINS

| Number of Animals  | Weight Before Treatment, gm | Weight After Treatment, gm | Ovarian Weight, mg | Uterine Weight, mg | Chorionic Gonadotropin Used |
|--|-----------------------------|----------------------------|--------------------|--------------------|-----------------------------|
| <i>Adrenotropin, 1 U, 0.625 U chorionic gonadotropin</i>   |                             |                            |                    |                    |                             |
| 7  | 34.0                        | 51.6                       | 9.4                | 26.0               | No                          |
| 7  | 30.0                        | 33.4                       | 13.0               | 108.0              | Yes                         |
| <i>Thyrotropin, 1.25 U, 0.625 U chorionic gonadotropin</i>   |                             |                            |                    |                    |                             |
| 6  | 28.6                        | 32.1                       | 9.1                | 19.8               | No                          |
| 6  | 32.1                        | 35.8                       | 11.1               | 96.4               | Yes                         |
| <i>Lactogenic hormone, 5 U, 0.625 U chorionic gonadotropin</i>   |                             |                            |                    |                    |                             |
| 7  | 33.3                        | 46.4                       | 11.0               | 25.0               | No                          |
| 7  | 29.0                        | 33.0                       | 14.0               | 132.0              | Yes                         |
| <i>Growth hormone preparation, 1 U, 0.625 U chorionic gonadotropin</i>                                 |                             |                            |                    |                    |                             |
| 6  | 32.0                        | 36.0                       | 8.0                | 24.8               | No                          |
| 6  | 35.0                        | 36.0                       | 14.0               | 94.5               | Yes                         |
| <i>Adrenotropin, 1 U, lactogenic hormone, 5 U, 0.625 U chorionic gonadotropin</i>                      |                             |                            |                    |                    |                             |
| 5  | 36.2                        | 32.4                       | 7.1                | 22.3               | No                          |
| 5  | 35.4                        | 33.6                       | 13.1               | 135.1              | Yes                         |
| <i>Adrenotropin, 1 U, lactogenic hormone, 5 U, thyrotropin, 1.25 U, 0.625 U chorionic gonadotropin</i> |                             |                            |                    |                    |                             |
| 5  | 33.2                        | 34.5                       | 6.6                | 20.7               | No                          |
| 5  | 36.0                        | 38.0                       | 9.4                | 41.4               | Yes                         |

addition of 1.25 units of thyrotropin. This combination was given again with and without chorionic gonadotropin.

The figures in the tables seem to show that injections of these varied pituitary factors, alone or in combination, produce a definite increase of uterine weight as an expression of their synergism with the chorionic gonadotropin. The increase in the weight of the ovary is almost negligible. The most impressive increase in uterine weight, 112.8 mg, was obtained by the combination of adrenotropin-lactogenic treatment, that with lactogen closely followed, being 107 mg. The lowest values were obtained in the series which received the thyrotropin in combination with the adrenotropin-lactogen mixture, suggesting the possibility that thyrotropin acted as a depressor upon the synergistic mechanism.

Histological examination of the ovaries revealed only a slight degree of follicular stimulation. How-

ever, one or two lutein bodies were found in each ovary, some fairly well developed, others in the incipient stage of luteinization. There is no doubt that our synergistic combinations do not affect the uterus directly, for no uterine response was obtained in castrated, immature females. We also injected some castrate rats with various dilutions of an estrone solution.<sup>4</sup> Six 1 U of estrone were needed to produce a uterine weight of 36.7 mg and 25 for an increase to 57.3 mg as compared with the uterine weight of the untreated control castrates which averaged 16.7 mg. Addition of the various pituitary factors, or of the unfractionated extract with or without chorionic gonadotropin, did not increase the uterine weights of the castrate rats treated with estrone, regardless of whether the estrone was given on the 2, 6 or 25 1 U dosage level. These observations confirm the view that the synergistic effects take place in the ovary.

<sup>4</sup>The estrone (Theelin) was supplied by Parke, Davis & Co., Detroit, Mich.

and any changes of the uteri are the results of the production of ovarian hormones. It seems, however, that ovarian size is not an absolute criterion of ovarian secretory activity since it is possible to obtain substantial uterine responses without far-reaching changes of ovarian structure.

The presence of pituitary gonadotropin in the various extracts used must be considered as a possible explanation of the effects observed. However, the marked augmentation of effects with the small amounts of chorionic gonadotropin would make it necessary to postulate a concentration of gonadotropins to a degree which is incompatible with the complete ineffectiveness of these extracts if used alone. The assumption, moreover, that the thyrotropic extract owed its synergistic potency to the presence of gonadotropin in significant amounts, is contradicted by the fact that its addition to the lactogenic-adrenotropin-chorionic gonadotropin mixture elicited a drop of uterine weight from 135 to 41 mg., instead of further augmentation.

#### SUMMARY

Synergistic effects, similar to those obtained by the combination of unfractionated anterior lobe extracts or Collip's 'specific metabolic principle' with chorionic gonadotropin, are demonstrable if purified pituitary fractions are combined with chorionic gonadotropin. Adrenotropin, thyrotropin, lactogenic hormone, 'growth extracts' and combinations of adrenotropin and lactogen, as well as adrenotropin, lac-

togenic hormone and thyrotropin were used. Increase of uterine weight, comparable to that previously reported, was observed although the ovaries did not show significant enlargement.

As the synergistic combination is ineffective in the castrate, in spite of administration of estrogen, it must be assumed that the effects are due to ovarian stimulation and production of ovarian hormones. Microscopic examination of the ovaries revealed slight follicular stimulation accompanied by localized luteinization.

Uterine response obtained with a minimum of ovarian changes appears to be a more physiologic reaction than uterine enlargement of the same or lesser degree preceded by extensive ovarian changes.

These findings are in accord with clinical experience which suggest that better therapeutic results are obtained if a lower dosage of the chorionic gonadotropin is used in combination with synergistically effective anterior lobe extracts.

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## COMMUNICATIONS TO THE EDITORS

### Use of Ethinyl Estradiol to Prevent Lactation in Puerperal Patients

ETHINYL ESTRADIOL was prepared by Inhoffen and Hohlweg<sup>1</sup> by the replacement of the 17th carbon atom in estradiol by an ethinyl group. When given subcutaneously in oil, ethinyl estradiol and estradiol are equal in potency, but when given orally, ethinyl estradiol is 15 to 20 times as active as estradiol. Clauberg and Ustun<sup>2</sup> reported the use of ethinyl estradiol in secondary amenorrhea and oligomenorrhea and demonstrated proliferative changes in the uterine mucosa following doses of 56 mg of ethinyl estradiol, given over a period of 20 days. No symptoms of toxicity were reported in their series. Salmon et al.<sup>3</sup> administered ethinyl estradiol in the form of enteric coated tablets and in alcoholic solution to 27 patients with menopausal symptoms and morphologic evidence of estrogen deficiency (tablets, 22 patients, alcoholic solution, 5 patients). Ethinyl estradiol in the form of enteric coated tablets was found to possess high estrogenic potency when administered orally, as demonstrated by the relief of menopausal symptoms and by the characteristic estrogenic changes induced in the vaginal mucosa. Nausea and vomiting occurred in 4 of the 22 patients taking the enteric coated tablets and in all 5 patients taking the alcoholic solution of the hormone. The side effects included abdominal pain and malaise, chills and vertigo.

We are reporting a series of 59 cases in which ethinyl estradiol was administered orally to puerperal women, in order to prevent lactation. These patients had no other form of therapy, no saline cathartics or limitation of fluids were employed. Breast support in the form of a brassiere was used in some cases. These cases can be divided into 3 groups, as follows:

**Group 1** The amount of ethinyl estradiol administered to 26 women was between 0.45 mg. to 0.90 mg. daily for 2 to 3 days. Medication was started 1 to 2 days post partum, except in 4 cases in which treatment was started on the 3rd, 4th, 6th and 56th day post partum, respectively. Of this group, 9 women had fullness of the breasts ranging from moderate to full engorgement, with lactation the general rule. In some of the patients, the engorgement did not begin until the 8th or 9th day, and even as late as the 14th day post partum. Poor results were obtained in two women in whom dead fetuses were carried 1 and 3 days ante partum, although treatment was not begun until after delivery. Results were good in 17 patients. In 12 women there was no secretion from the breasts

whatever, however, some of these patients may have lactated after going home on their 10th day post partum. This group was composed entirely of service patients, and followup study was difficult. Weaning of the baby at 8 weeks was entirely successful and satisfactory, the breast secretion disappearing within 72 hours, the dosage given was 0.90 mg. daily for 2 days.

**Group 2** The dosage given was between 1.35 and 2.40 mg of ethinyl estradiol daily for 3 days, beginning 1 to 2 days post partum. There were 16 patients in this group, and the results were excellent in 12 women. In 4 cases, there was some fullness of the breasts, but only in one case was there any marked engorgement or distress. This patient had received 1.80 mg. daily for 3 days beginning one day post partum.

**Group 3** The dosage of ethinyl estradiol was 1.80 to 2.40 mg given daily for 3 days, and started 4 to 21 days post partum. These women had, in most instances, already begun to nurse their babies, and breast feeding was discontinued for various reasons. There were no failures of therapy in this group. The breasts, if previously full and engorged, subsided within 24 to 36 hours. However, when there had been lactation already, there was continuance of milky secretion as a rule for 4 to 14 days. One patient continued to secrete for a month although there was no associated breast fullness or pain.

**Discussion** There seems no question that with administration of sufficient ethinyl estradiol, lactation either will be prevented entirely or controlled so well that the large majority of patients avoid the usual aftermath of symptoms, such as painful, engorged breasts, fever and discomfort. Some patients respond better than others, however, when the dosage given is between 1.80 and 2.40 mg daily for 3 days, good results can be expected in at least 90 per cent of the cases.

There were no toxic symptoms exhibited in any of these 59 patients, even though therapy was begun in one instance 3 weeks, and in another 8 weeks after delivery of the child. The drug was tolerated well, with no abdominal distress, nausea, vomiting or weakness.

**Summary** A series of 59 women, all puerperal, were given ethinyl estradiol orally, for 3 to 4 days.

When the amount given was below 1.5 mg. per day, results were only fair, with 9 failures in a series of 26 cases.

When 1.5 to 2.4 mg of ethinyl estradiol was given daily for 3 days and the medication was started 1 to 2 days post partum, the results were excellent in 12 cases. There was only one frank failure.

When the dosage was 1.80 to 2.40 mg. daily for 3 to 4 days, given 4 to 21 days post partum, relief was quickly obtained, and the results very satisfactory.

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The ethinyl estradiol was supplied by the Schering Corp., Bloomfield, N. J.

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# EDITORIALS

## CHONDRO-EPIPHYSITIS AS A MANIFESTATION OF THYROID DEFICIENCY

THAT THE THYROID hormone has a stimulating effect on cells throughout the body has long been a medical truism. A necessary corollary to that generalization, however, has often been overlooked. Deficiency of thyroid secretion must necessarily affect the chemical processes, hence the vitality, of all organs and tissues. If no particular organ or system is particularly vulnerable, the result is likely to be a condition of 'general poor health' to use McLester's characterization. When, however, some one part of system is, for genetic or other reason, of less than proportionate intrinsic vigor it is likely to be more affected than other parts of the body. In the older terminology it becomes a *locus minoris resistentiae*. This principle seems to account for the fact that thyroid deficiency may be manifested in numerous sorts of symptomatology—sorts that seem, at first thought to be too dissimilar to have resulted from a common etiological factor.

As was brought out strikingly in a symposium on the relation of the endocrines to skeletal development at the recent Atlantic City meeting of the Association the epiphyseal structures are exquisitely responsive to hormonal influences. The influence of the thyroid hormone is emphasized in a recent article by Schaefer and Purcell.<sup>1</sup> These authors, following recent usage, bring together under the term 'juvenile chondro epiphysitis' a number of disorders which have appeared under a variety of names such as Legg-Perthes disease, Osgood Schlatter disease and Scheuermann disease, the specific term referring to the site of manifestation. They do not, however, indicate any essential difference in the fundamental nature of the disorders. The etiology has long been uncertain. Trauma, infection, toxemia, heredity or other factors have been postulated as causes but without convincing evidence of the fundamental etiological importance of any.

The authors report a detailed study of 27 cases of chondro epiphysitis in which remarkable improvement was seen when thyroid, in adequate dosage, was administered. As accessory measures, ambulatory general management and reduction of obesity were emphasized. Anterior pituitary preparations were also given in some cases when those were regarded as specifically indicated. The patients ranged in age from 5 to 16 years and the dosage from 2 to 3 grains of desiccated thyroid daily. The period of treatment extended in various cases from 2 months to 4 years.

The current methods of immobilization and orthopedic treatment are condemned. The conviction is expressed that the proper basic treatment is adequate thyroid therapy. In consonance with this conclusion the authors propose discarding the confusing terminology of proper names as related to the various joints involved and suggest the term 'ostochondreal hypothyroidism' as more descriptive and as accurately applying to all of the varieties.

It should be added that the authors confine their discussion to juvenile ostochondreal hypothyroidism, excluding such adult manifestations as Kienbock's disease and osteo-chondritis dissecans.

R G H

## AMINO-ACID FACTOR IN MALE FECUNDITY

FOR MANY YEARS clinicians have recognized that obesity is likely to be associated with low fecundity. Since the subjects appear to be over-nourished, the fact that they frequently suffer from protein food deficiency is often overlooked. Indeed, the very obesity itself is sometimes, in part at least, to be ascribed to the lack of the specific dynamic action of protein metabolites. Poultrymen and stock breeders have long known that some protein foods are more valuable than others in promoting both vigor and fecundity. The part played by the individual amino acids in determining the biological value of proteins as related to fecundity has recently come under new study.

At the 1942 meeting of the Federation of American Societies for Experimental Biology, L. Emmett Holt and collaborators of the Department of Pediatrics, Johns Hopkins University Medical School, reported an investigation of some of the effects of amino acid deficiency in man. Four men and one woman volunteered to serve as subjects over periods in which different amino acid deficiencies were established. The lack of both tryptophan and lysine were found to result in negative nitrogen balance which persisted throughout the experimental period, except that the female subject was able to maintain the balance for a brief period preceding the onset of menstruation. When 3 of the subjects were given arginine for 10 days, they were able to maintain nitrogen equilibrium but a prompt deleterious influence upon the gonads occurred. On the 9th day of the experiment the spermatozoal count had been reduced to 0.1 of the normal value. On a similar diet, but containing arginine, the sperm cell count began to improve at once. Several weeks on a normal diet, however, were required for complete restoration.

R G H.

<sup>1</sup> SCHAEFER, R. L., AND F. H. PURCELL. *Am J Surg* 54 589 1941

# Abstracts of

## CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. Collaborators: E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLIN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

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### ENDOCRINE GENERAL

BENNETT, H. G., AND R. W. TE LINDE

The menopausal syndrome. Treatment with the implantation of crystalline estrone pellets.

Satisfactory relief of symptoms with theelin pellets occurred in 93% of the patients treated while diethylstilbestrol pellets gave 100% of relief. Abnormal bleeding occurred in 3.5% of the theelin treated patients while 72% of the diethylstilbestrol patients had abnormal bleeding. Of the seven forms of therapy tried the implantation of crystalline estrone pellets was the best.—C.P.

BRONSTEIN, I. P., S. WEXLER, A. W. BROWN AND L. J. HALPERN.

Obesity in childhood. Psychological studies. *Am. J. Dis. Child.*, 63: 238, 1942.

Comprehensive physical studies of 35 obese children did not reveal any ascertainable evidence of any endocrine basis for the condition. The mean intelligence of this group was above the mean of the population as a whole and achievement tests showed little or no difference from children of similar capacity. Only 2 of the group showed a tendency toward femininity. There was a definite tendency to be sensitive about their obesity, toward extroversion and instability and an interest in sedentary play activities.—M.B.G.

BUNKLEY, T. F.

Uterine bleeding complicating pregnancy. Its significance as shown in one hundred consecutive cases. *Texas State J. Med.* 37: 672. 1942.

In 100 consecutive cases of uterine bleeding occurring during pregnancy, 63 cases occurred during the first trimester, 22 during the second, and 19 during the third.

Thirty-two cases of hemorrhage occurred with no pain at any time. During the first two trimesters there were 51 cases of threatened or inevitable abortion and 25 cases of ectopic pregnancy. The other cases of bleeding occurred chiefly during the last four months, representing 15 definite abnormal conditions, including 8 cases of placenta praevia and 4 abruptio placentae. Of the 19 cases of bleeding occurring during the last trimester, there were 14 live babies. In this series there were 3 maternal deaths, 2 in the last trimester as result of uterine atony, and 1 during the first trimester due to ectopic pregnancy complicated by chronic nephritis.

The conclusion drawn indicates that bleeding during pregnancy in any stage is a symptom of trouble of some kind and in the majority of cases is serious either to the fetus or the mother. During the third trimester bleeding of any severe type may be fatal to both the mother and the baby.—Author's summary.

FINCH, J. WILLIAM.

The nausea and vomiting following administration of diethylstilbestrol. *Jour. A.M.A.* 119: 400. 1942.

The nausea and emesis accompanying diethylstilbestrol therapy is similar to if not identical with that of early pregnancy. The author believes this is an allergic response and desensitization with small but gradually increasing doses results eventually in the full therapeutic dose being well tolerated.—C.P.

HAIN, A. M.

Further observations on the role of progesterone (pregnanediol) and oestrogen in pregnancy. *J. Endocrinol.* 3: 10. 1942.

The progesterone excretion (pregnanediol) of over 100 women with histories of previous miscarriages or anomalies was ascertained throughout a pregnancy in which some form of therapy was usually administered. The common theory that parturition and abortion are due to the waning secretion of progesterone was found untenable, as both conditions were frequently accompanied by levels of pregnanediol output associated with a continuance of pregnancy. Also in over 60% of women in whom symptoms of threatened abortion were present the outputs of both gonadotropin and pregnanediol were such as characterize normal pregnancy. However, pregnancy was capable of being maintained by even small amounts of progesterone as was shown by the degree of fetal development reached by patients in whom abortion occurred at low levels of pregnanediol excretion. It is concluded that a factor making for abortion (or parturition) comes into play which progesterone is powerless to inhibit. The possibility that this was a rise in free estrogen was investigated but not substantiated. Other possibilities are discussed and evidence is given of an extraneous factor exercising a rhythmic control of hormone excretion at the approach of parturition. The data afforded information as to secretory types and the prognostic value of the analyses, and permitted a comparison to be made of the values of vitamin E and progesterone therapy in threatened and habitual abortion; the importance of rest was stressed.—Author's summary.

JOHNSTON, MARGARET W., AND L. H. NEWBURGH

Calculation of heat production from insensible loss of weight *J Clin Investigation* 21 357 1942

Indirect calorimetry i.e. the calculation of heat production by the measurement of vaporization provides satisfactory values provided that suitable factors for the translation of weight into heat are employed. These factors depend upon the type of diet fed: 57 for the low carbohydrate diet, 50 for the high carbohydrate diet and 53 for the normal or ordinary diet. These factors multiplied by the hourly insensible weight loss will give a satisfactory prediction of the 24 hour heat production.—B.B.R.

KALTREIFF, N. L., G. R. MENEELY, AND J. R. ALLEN

The effect of epinephrine on the volume of the blood *J Clin Investigation* 21 339 1942

Plasma volume was determined from the disappearance slope of injected azo blue T 1824 in six normal subjects, two patients with polycythemia vera, and in two splenectomized patients. In the normal individuals following the injection of 1 cc of epinephrine 1-1000 the plasma volume decreased approximately 5%, and the red cell count increased about 2%. The pulse rate and systolic blood pressure was increased while the diastolic blood pressure diminished. Similar findings occurred also in the patients with polycythemia vera, while after splenectomy the decrease in plasma volume after epinephrine is accompanied by a diminution in red cell count. The injection of epinephrine in normal individuals thus resembles the effects of severe exercise.—B.B.R.

McLAREN, H. C.

The normal menopause *J Obst & Gynaec Brit Emp* 48 1 1941

A study of 84 patients (average age 63) who had undergone a normal menopause refuted the generally accepted statement that atrophy of the genital tract with thinning of the vaginal mucosa is the usual sequel to the climacteric. Histological examination of the vagina revealed that 65% were normal in appearance. Grade III smears (predominantly composed of squamous cells) were found in 78%. A pure growth of Doderlein's bacillus was present in 28%, and in 8% there was secretion with a pH of less than 5. Evidently in many females little anatomical or physiological change occurs in the postmenopausal vagina, except for an occasional rise in pH with an influx of mixed organisms. The findings provided confirmatory evidence of ovarian activity after the menopause.—H.O.H.

McLAREN, H. C.

The induced menopause *J Obst & Gynaec Brit Emp* 48 23 1941

Examination of 214 cases of induced menopause (100 radium treated, at least 2400 mg. hours, 39 hysterectomy oophorectomy, 36 hysterectomy unilateral oophorectomy, 39 hysterectomy) revealed that flushing occurred in about 1/2 of the radium and castrated groups, but was rare in

patients following hysterectomy with preservation of ovarian tissue. No marked changes occurred in the external genitalia. Mucosal atrophy of the vagina occurred in 14% of the radium group, 28% of the castrated group, 3% of the surgical group with retained ovarian tissue. Upper vaginal stenosis was common in the radium group. No relation existed between the severity of menopausal symptoms and the type of vaginal smear or mucosa. The use of the vaginal smear as an index of the success of estrin therapy proved indefensible.—H.O.H.

MOEHLIG, R. C., AND L. JAFFE

Syndrome simulating diabetes insipidus in dogs induced by desoxycorticosterone acetate *J Lab & Clin Med* 27 1009 1942

Two of five dogs receiving 5-10 mg. of desoxycorticosterone acetate daily over a period of four months developed a syndrome of polydipsia and polyuria, and one of them died. Muscular weakness and tetany were prominent features in all five dogs. Microscopic sections of the hypothalamus showed localized encephalitis. A patient suffering from myasthenia gravis received multiple pellet implantation totaling 1300 mg. of doca. Within two weeks he too developed marked polydipsia and polyuria and spontaneous tetany. The symptoms diminished in severity over a three month period, since when the patient has felt stronger than at any time since the onset of his illness. Thus tetany, polydipsia, and polyuria may be considered toxic manifestations of over dosage with doca.—B.B.R.

MUKHERJEE, C.

The posterior pituitary factor in toxemias of pregnancy *J Obst & Gynaec Brit Emp* 48 586 1941

Experimental observations, using blood ultrafiltrates of 50 unselected cases of toxemias of pregnancy, revealed a substance which showed melanophoric, antidiuretic, and vasopressor properties, as tested in the frog, the guinea-pig, and the cat, respectively. The reaction of the toxemic subject to injection of vasopressin was greater and more sustained than that of the normal pregnant female. Toxic symptoms in normal pregnancy required massive doses of vasopressin, whereas a single small dose (1/4 cc.) produced marked toxic manifestations under conditions of pregnancy toxemia. These facts, together with the observation that in the eclamptic subject injections of vasopressin elicited a blood pressure rise quite out of proportion to size of dose, led to the concept of a high concentration of the pressor hormone in the circulation, with perhaps a hypersusceptibility on the part of the patient. A functional hyperactivity of the posterior lobe in toxemic states is postulated.—H.O.H.

SAPHIR, W., AND A. R. WEINGLASS

Severe angioneurotic edema following diethylstilbestrol therapy *J Am Med Assoc* 119 557 1942

Diethylstilbestrol at a dosage level of 0.5 mgm. daily for 6 days produced severe allergic edema in a 53 year old menopausal female. After mild edema of the hand and foot, severe edema of the lips, face, neck and tongue appeared



Fearing edema of the glottis the patient was hospitalized but the symptoms subsided in 24 hours. Intradermal tests with 0.1 cc. of a 1:10,000 solution were positive.—C.P.

STERNBERG, W. H., AND V. JOSEPH.

Osteodystrophia fibrosa combined with precocious puberty and exophthalmic goiter. Pathological report of a case. *Am. J. Dis. Child.* 63: 748. 1942.

About 26 probable cases have been reported of the syndrome characterized by asymmetric diseases of bones, melanotic pigmentation and precocious puberty in females. A similar syndrome without precocious puberty occurs less frequently in males. The authors report what they consider to be the first complete pathological observations of this syndrome. The clinical aspects of the case were reported by McCune and Bruch (*Am. J. Dis. Child.* 54: 806. 1937).

The disease of the bones is patchy and is characterized by lacunar osteoclastic resorption, fibrosis of marrow spaces, osteoblastic repair and cyst formation. The presence of islands of cartilage with bone formation at their peripheries is looked on as an extreme effort at repair. The pathologic picture resembles von Recklinghausen's disease although the tempo of bone resorption is slower and hyperparathyroidism is not present.

The important endocrine findings were a hyperplastic thyroid, thymus and lymphoid structure, mature cystic ovaries with no evidence of luteinization, a narrow, lean adrenal cortex, and parathyroids within normal limits. The pituitary showed basophilic hyperplasia with adenoma formation.—M.B.G.

SULLIVAN, J. M., AND R. A. MUNSLOW.

Gynecomastia. A study of five cases. *J. Am. Med. Assoc.* 118: 1443. 1942.

Five cases of gynecomastia in soldiers are presented in which the chief complaint was inability to wear a pack. While the onset of the swelling was during adolescence, no accompanying endocrine symptoms were present. The pathological changes were histologically similar to those of chronic cystic mastitis.—C.P.

VIETS, H. R., R. S. SCHWAB AND M. A. B. BRAZIER.

The effect of pregnancy on the course of myasthenia gravis. *J. Am. Med. Assoc.* 119: 236. 1942.

After reviewing equivocal data from approximately 20 cases in the literature, the author adds the case histories of eight myasthenic patients who have undergone preg-

nancy and concludes that the effect of pregnancy on myasthenia is usually favorable. Exacerbation if it occurs is usually in the first trimester while amelioration occurs in the second and third trimester and extends for 3 to 6 months after delivery.—C.P.

ZONDEK, BERNHARD.

Simplified hormonal treatment of amenorrhea. *J. Am. Med. Assoc.* 118: 705. 1942.

The simplified treatment of amenorrhea for the general practitioner is outlined as follows:

1. Secondary amenorrhea of 2 years duration—50 mg. progesterone over two to five days.
2. Less than two years duration—25 mg. progesterone with 2.5 to 5.0 mg. estradiol benzoate over a period of two days.
3. Primary and castration amenorrhea—50 mg. progesterone with 2.5 to 5.0 mg. of estradiol benzoate in 5 days.—C.P.

## PANCREAS

BARNES, H. H. F.

Diabetes mellitus and pregnancy. *J. Obst. & Gynaec. Brit. Emp.* 48: 707. 1941.

A review of 25 diabetic pregnancies in 21 patients revealed the average age at onset of diabetes to be 31 years; the average age at which pregnancy supervened to be 33 years. Insulin requirements increased in 74% of cases as pregnancy progressed. The maternal prognosis was good and pregnancy did not aggravate the diabetes if the latter was adequately handled. Fetal mortality was 44%. Toxemia of late pregnancy was held the chief cause of intra-uterine death, twice as lethal to the fetus of the diabetic subject as to that of the non-diabetic female. Hypoglycemia was not found in any of the live infants. However, administration of extra sugar in early neonatal life is advised to counteract any possibility of this complication. Management of the pregnant diabetic is outlined.—H.O.H.

LUETSCHER, J. A. JR.

Metabolism of amino acid in diabetes mellitus. *J. Clin. Investigation* 21: 275. 1942.

In a group of twelve severe untreated diabetics high plasma levels of amino acids accompanied by increased urinary excretion of amino acids were found. Insulin therapy reduced the blood and urinary excretion to normal levels which were maintained despite fluctuations in the blood sugar and urinary sugar excretion.—B.B.R.



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## Acromegaly: A Consideration of Its Course and Treatment

Report of Four Cases with Autopsies

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### [[Pituitary Adenoma]]

IN THE FINAL analysis it is long personal familiarity with, and a critical discriminating attitude toward, a wealth of clinical material that add a modicum of authoritative information to the sum of our knowledge of a given disease. Lack of opportunity to fulfill these requirements probably accounts for the fact that very little has been added to our knowledge of acromegaly since the comprehensive work of Cushing and Davidoff (1-5) was published nearly 15 years ago. Although many of their conclusions were hypothetical at the time, they have since been substantiated in the light of newer knowledge concerning the pituitary gland. Their analysis included 100 verified cases, a truly sizeable series considering the rarity of the disease. Up to 1938, Atkinson (6, 7, 8), after diligent search of the literature and with the aid of the British Consular Service all over the world, had been able to uncover only 1606 cases of acromegaly which he tabulated in a unique monograph. Approximately 55 additional cases which were reported during the past 4 years have brought the total to 1661. Autopsies have been performed in less than one fourth of these. At the University of California Hospital, over a 5 year period from 1937-1941, 12 cases have been so diagnosed among 35,757 entries, or in inci-

dence of 1 in 3000. This figure is rather different from that reported by the Boston City Hospital for a 6 year period from 1930 to 1935, during which time the diagnosis of acromegaly was made in 14 cases among 210,094 entries, or an incidence of 1 in 15,000.

This bizarre malady is not only rare but it is also impressive in its manifestations, protean in its symptomatology, and kaleidoscopic in its involvement of more tissues and organs than almost any other disease. The onset is likely to be insidious, the course usually is chronic and of long duration and is marked by successive waves of remissions and exacerbations. These characteristics combine to render difficult the clear evaluation of the findings in a single case and, even more so, of the efficacy of any specific form of treatment. One dare not theorize or draw sweeping conclusions from one or two cases. Even the post-mortem observations may be misleading unless a correlation has been established between them and the clinical status at the time of death.

In this paper we are reporting the cases of four acromegals whom we have had the opportunity to follow for an extended period of time and in whom autopsies were performed. Three are from the Out-Patient Department of the University of California Hospital and one is from the Out-Patient Department

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of the Hospital for Women and Children. A review of the histories leaves us dissatisfied with the therapeutic results achieved and convinces us that, in distinction from the neurological aspects, the more pervasive endocrinological derangements of this disease are not receiving the attention they deserve. It seems to us desirable, therefore, to record the course of the disease in these four patients and to discuss what might have been accomplished by earlier and more vigorous therapy.

#### CASE REPORTS

*Case 1 (U. C. H. No. 1707).* Progressive acromegaly of 17 years' duration in a man, treated by pituitary irradiation in inadequate amounts. Subtotal hypophysectomy, urged in the early stages of the disease to prevent further deformity and the possible development of diabetes mellitus, was refused. Diabetes mellitus developed 6 months prior to death which occurred at age 37 from gas and oxygen anesthesia preparatory to resection of a pilonidal cyst. An enlarged thymus was found at autopsy.

A 23-year-old unmarried student mechanic presented himself at the Out-Patient Department of the University of California Hospital on Dec. 17, 1923, with a complaint of severe frontal headache of 6 months' duration. For at least 3 years he had noticed gradual coarsening of his features, protrusion of the lower jaw, increasing spacing of his teeth with attendant difficulty in chewing and gradual enlargement of his hands both in thickness and in width. He had no visual disturbances except transient diplopia on removing his glasses. He perspired profusely but had no night sweats. He had no polyuria or polydipsia; however, he complained of a sense of fullness in the epigastrium and of chronic constipation. A stereoroentgenograph of the skull which had been taken several months previously showed enlargement of the sella turcica in all diameters and slight thinning of the posterior clinoids. The patient had received 12 roentgen-ray treatments to the pituitary, the last one 2 weeks before he presented himself, but his headache had, as yet, not been alleviated.

The only significant factor in the family history was that the patient's mother was said to have died of liver disease, diabetes and hypertension. The patient was born in Siberia. In addition to the usual childhood diseases he had typhus fever at the age of 16 and a Neisserian infection at the age of 20. Also, during his 20th year a hernioplasty was done on the left side. One year later the resultant hypertrophied scar was excised and a tonsillectomy was done. These apparently irrelevant operations are significant in view of the nature of the patient's death during anesthesia 17 years later.

Physical examination revealed a short, stocky, muscular, swarthy and hirsute young man, (fig. 1, *D* and 1, *F*), with coarse features, large, heavy zygomatic processes, protruding lower jaw and widely spaced teeth (fig. 1, *C*). The height was 65.5 in. (166.5 cm.), the weight 164 lb. (74.5 kg.) and the blood pressure 110 mm. Hg systolic and

64 diastolic. In contrast to the muscular development, the lack of strength was striking. Other noteworthy findings were moderate anterior cervical lymphadenopathy, an extensive birthmark on the left thigh, and typically spade-like hands with marked hypotonicity of the fingers. Of importance also was the fact that the eyegrounds and visual fields appeared normal.

Roentgenograms of the skull showed a large, globular sella turcica, markedly hypertrophied mandible, slightly hypertrophied maxilla, enlarged antra, and prominent glabella without thickening of the cranial bones. The blood Wassermann reaction was negative; the B.M.R. was -5.9 per cent. The urine showed a specific gravity of 1.020; it contained no albumin or sugar and was normal microscopically.

Because the patient had recently received roentgen-ray therapy, treatment was confined to administration of desiccated thyroid substance, in doses of 1 grain 2 times daily, and reduction of caloric intake. In April, 1924, 4 months later, the headaches were still unrelieved but he had lost 11 lb. in weight (5 kg.) and the hands and fingers were less puffy. We then lost contact with him for 4 years. He again reported on May 21, 1928, stating that although the headaches had disappeared, prognathism and dental spacing were increasing, his eyesight had become impaired and he was troubled with backache. Upon examination the vision in the right eye was 20/20; in the left, 20/30. The fundi of both eyes revealed physiological cupping and slight temporal pallor. The visual fields were slightly flattened in the upper and outer quadrants. The B.M.R. was -9.3 per cent. Blood cholesterol was 216 mg. per cent. The glucose tolerance curve showed fasting blood sugar expressed in mg. per cent of 93; ½ hr., 126; 1 hr., 178; 2 hr., 169; the urine showed 1+ sugar in the 2-hr. specimen. Because of the suggestive blood-sugar curve, the patient was referred to the diabetic clinic for dietary control.

Despite this attempt at control, when the patient was seen one year later (May, 1929) the weight had increased to 206 lb. (93.6 kg.), a gain of 42 lb. over a 5-year period. The lower jaw protruded .5 in. anterior to the upper and showed increased spacing of the teeth. The hands and feet had become broader. He claimed that libido had increased markedly but that he had indulged in intercourse only once in 8 years because of 'fear of venereal infection.' The visual acuity had decreased (20/40 in the right eye and 20/70 in the left eye.) The fundi appeared unchanged but the visual fields, especially the left, showed definite restriction (fig. 2, *A*). Because of the beginning impairment of vision, sellar decompression was strongly considered. However, pituitary irradiation was given, instead, with the understanding that if no improvement resulted surgical intervention would be urged. After only 4 roentgen-ray treatments (approximately 625 r to each side<sup>1</sup>) the patient failed to return.

When the patient again reported in October, 1931, 2.5 yr. later, the weight and blood pressure were the same as before. Prognathism and spacing of teeth had increased but the size of the feet had remained unchanged. The backache which he had had for 7 years persisted. A roentgeno-

<sup>1</sup> For full details of roentgen-ray dosage see *Addenda, synopsis of roentgen-ray therapy, case 1.*

gram of the spine taken in 1926 had shown that the articular facets of the lumbar region were somewhat irregular and that the joint spaces were not clear. In a film taken at this time the appearance of both sacro iliac joints was irregular and suggested continuous growth rather than

eyes was considered as stationary. No disturbance of taste or smell could be elicited. The urine contained no sugar. The blood revealed a secondary anemia (Hb 70%, R B C 3,320,000, W B C 6,600, with polymorphonuclear leucocytes 65%, lymphocytes 28%, monocytes 5%.

Fig 1 PROGRESSION OF ACROMEGALIC STIGMATA OVER 17 YEARS, case 1. A, at 16 years of age, before onset. B, at 20 years showing first evidence of slight coarsening of features. C, age, 23 years when first seen. Note deepening of forehead and nasolabial folds, thickening of end of nose, spacing of teeth and broadening of wrist and fingers.

D and F, age 23. E and G, age 37, note broadening and deepening of chest, hirsutism, further heaviness and coarsening of features and increased prognathism. Gain of 40 lb in weight. Characteristic cervico dorsal kyphosis is absent.



arthritic changes. The patient himself called attention to the progressive sternal bulging which necessitated the purchase of increasingly larger coats. He was still suffering from excessive perspiration and experienced drenching night sweats. Asthenia had been progressive. Lateral vision was somewhat limited, especially on the right, but he had no diplopia or photophobia. Although partial bilateral optic atrophy was noted, the visual fields had not changed appreciably since 1929 and the process in the

transitorials 2% and eosinophiles 3%). The roentgenologist described the films of the skull (fig 3) as follows:

The cranium proper is within normal limits as to size and shape. The sella turcica is deformed by an upward displacement and tilting of the anterior clinoid processes, a posterior displacement of the posterior processes and dorsum sellae, and a depression of the floor to a level below that of the sphenoidal sinus. The frontal sinus is large and the cranium anterior to it is thickened and protuberant. The mandible is enlarged throughout. The vertical portion is so long that dental occlusion is impossible and

the horizontal ramus projects forward so that the lower incisors are considerably anterior to the upper. The latter are obliquely placed apparently in an attempt to reach forward to the lower incisors. The structure of the bone of the mandible and alveolar portion of the maxilla is slightly coarser than normal. A crude estimate of the volume of space occupied by the sella turcica is about 3 to 4 times greater than normal.

Repeated assays of the urine during the preceding 2 years for the presence of anterior pituitary growth hormone were carried out in the laboratory of Dr. Herbert

January, 1937, to the proctology clinic because he had a tender, painful swelling at the end of the spine which proved to be an infected pilonidal cyst. From comparison of the photographs taken in 1924 and those taken in 1937 (fig. 1, D, 1, E, 1, F, and 1 G), it was obvious that the characteristic acromegalic stigmata had progressed materially during the intervening years although no noteworthy change had occurred in the visual fields (fig. 2, B). Urinalysis disclosed glycosuria for the first time and the

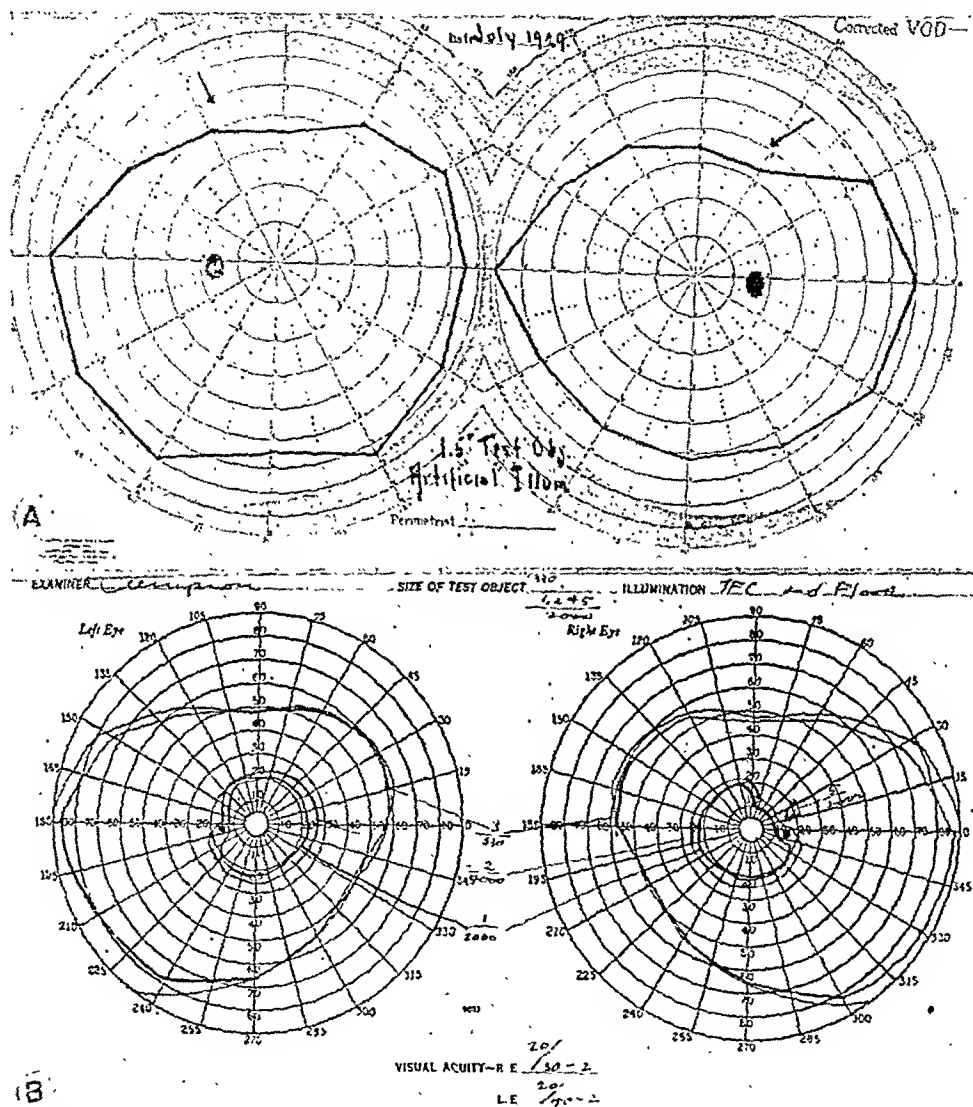


Fig. 2. PERIMETRIC CHARTS OF case 1. A, age, 29 yr. Note slight flattening of upper outer quadrants. B, age, 37 yr., shortly before death. Practically no change occurred in 8 years.

M Evans<sup>2</sup> and had been negative. By this time it was apparent that symptomatically and objectively the endocrinopathy had progressed steadily although the headache had disappeared and visual impairment had become stationary. The patient was warned that more serious complications, notably diabetes, might develop and was urged to submit to a partial hypophysectomy. Since he refused, additional pituitary irradiation was given, a total of 2100 r in 1931 and 3600 r in 1934.

After an absence of 2.5 years, the patient reported in

<sup>2</sup> Institute of Experimental Biology, University of California, Berkeley.

fasting blood sugar was 329 mg. per cent. Polydipsia and polyuria had been present for about 3 months. The last glucose tolerance test, performed in November, 1933, had shown the following results expressed in mg. per cent: fasting blood sugar, 102; ½ hr., 101; 1 hr., 145; and 2 hr. 168. B.M.R. was +11 per cent. Roentgenograms of the skull showed almost no change in 6 years. Roentgenograms of the hands showed increased arthritic changes at the margins of the phalangeal joints. Tufting was seen laterally, but not on the palmar or dorsal aspects. An osteochondroma had developed on the inner aspect of the upper end of the right tibia. Since an attempt to con-

trol the diabetes while the patient was ambulatory proved unsuccessful, he was admitted to the hospital on April 13, 1939. Laboratory studies made at that time showed blood serum calcium, 10.2 mg per cent, blood serum phosphorus, 5.38 mg per cent, plasma cholesterol, 264.0 mg per cent. The glucose tolerance test was interpreted as indicating a high renal threshold for glucose, the readings in mg per cent were as follows: fasting blood sugar, 215, at  $\frac{1}{2}$  hr, 263, 1 hr, 330, 2 hr, 348, 3 hr, 330, 4 hr, 308, 5 hr, 230 and 6 hr, 286. All urine specimens were negative for sugar save the 2 and 3 hr specimens which gave an olive reduction to Benedict's solution. When the patient left the hospital, for personal reasons, on April 19, the urine was sugar free. The diet consisted of carbohydrate, 150 gm, protein, 90 gm, and fat, 100 gm. The insulin dose was 30.0 20 u.

The patient re entered the hospital on April 23, 1937, and was placed on a preoperative diabetic regime. The urine and blood analyses at this time were normal. The heart measured 15 cm to the left in the fifth interspace. The heart sounds were of fair quality. Blood pressure in mm Hg was 110 systolic, 80 diastolic and pulse rate, 56. On April 26 the patient was taken to surgery for excision of the pilonidal cyst. Gas and oxygen anesthesia was begun at 3:20 p.m. The patient was asleep within 3 minutes. Before the incision was made he suddenly stopped breathing. Artificial respiration, adrenalin and caffeine administered hypodermically and metrazol intravenously were of no avail.

#### Autopsy

Because this death apparently resulted from the anesthesia, the necropsy was performed by Dr. Jesse Carr of the Coroner's Office on April 26, 1937.

**Gross findings.** The skull showed marked occipital thickening. The brain evidenced generalized softening. The hypophysis, which was about the size of an English walnut, was smooth, gray and homogeneous with a few areas of degeneration. It lay on the optic chiasm. The left side of the sella turcica was eroded but the right side was intact. The dependent portion of the gland showed a large degenerating mass of tissue which made it impossible to remove the gland intact. The lungs were edematous and partially collapsed. The heart weighed 451 gm (normal 350 gm) and was normal except for moderately sclerotic vessels. It did not show the petechiae of respiratory failure. The liver was reddish brown and congested. The spleen and pancreas were congested. The stomach was normal. The kidneys were normal except for slight congestion. Both adrenals were long, somewhat flattened and appeared enlarged. The prostate and bladder were normal. The thyroid was not palpable. The thymus was approximately 4 times normal size.

**Microscopic findings.** The heart muscle was edematous but otherwise normal. The lungs showed diffuse edema but no consolidation. The liver presented the appearance of cloudy swelling and some congestion. The spleen and kidneys were moderately congested. The cortical zones of the adrenals were clearly marked and showed deposits of lipid throughout. One cortical adenoma about 2 mm in diameter was seen. The medulla was definitely thickened and hyperplastic. The pituitary was increased in size because of the presence of an adenomatous overgrowth

characterized by an extremely dense cellular background of eosinophilic cells (fig 4, A). Neither fibrosis nor inter-acinar lymphocytes (which are so often found in thyroid glands that have been treated by roentgen-ray) were seen. The thymus appeared normal although some of Hassall's corpuscles were unusually large. Unfortunately the appearance of the thyroid, pancreas and testicles was unreported.

The pathological diagnoses were eosinophilic adenoma of the pituitary with acromegaly, acute pulmonary edema,



Fig 3. ROENTGENOGRAM OF SKULL OF CASE 1. Note large sella turcica with depression of floor and displacement of clinoids, large sinuses, marked prognathism and malocclusion.

congestion of viscera, pilonidal cyst, thymic hyperplasia, and hyperplasia of the adrenals with cortical adenomata.

#### Summary

This, then, is the record of an acromegalic who died at the age of 37 years, in the 17th year of the disease. The presenting complaint was headache which failed to yield to the roentgen ray therapy of that day (1924). The final disappearance of the cephalalgia after about a year may be attributed to spontaneous decompression of the tumor through erosion of the floor of the sella turcica. The course of the disease was characterized by steady progression of the endocrine manifestations despite roentgen ray therapy (which had consisted of an unknown amount during 1923 and 1924 and of about 7200 r between the years 1929 and 1934). Visual impairment was slowly progressive until 1929 but was held in check thereafter.

A noteworthy observation in this case is the late onset of diabetes which appeared only 6 months prior to death. An individual with active acromegaly apparently always is a potential diabetic. The patient

died a thymic death as a result of the induction of gas and oxygen anesthesia for excision of an infected pilonidal cyst. At autopsy an enlarged thymus was found. We might speculate whether the enlargement of the thymus was the result of its failure to involute or whether regeneration and hypertrophy of thymic tissue had been stimulated by the increased production of growth hormone from the hyperplastic eosinophilic adenoma of the pituitary. The fact that prior to the onset of the disease the patient had undergone

with a remarkable degree of visceromegaly but without evidence of diabetes mellitus or of increased intracranial pressure. Exitus at the age of 45 was due to degeneration of the anterior pituitary adenoma, purulent sphenoiditis and terminal bronchopneumonia.

The patient, a 31-year-old unmarried truck driver, first entered the University of California Hospital on June 6, 1922, because of facial and skeletal changes, impairment of hearing and inability to breathe through his nose. His family history was irrelevant. His past history was not



Fig. 4. A. EOSINOPHILIC ADENOMA OF HYPOPHYSIS of Case 1. Note highly cellular structure and absence of fibrosis despite pituitary irradiation.  $\times 90$ . B. THYMUS. Note unusually large Hassall's corpuscle.  $\times 90$ . The thymus was 3 to 4 times larger than normal for a man 37 years of age.

two surgical operations without untoward reactions would be an argument in favor of the latter hypothesis. The adrenals also were hyperplastic and showed minute cortical adenomata. The microscopic picture of the eosinophilic adenoma of the pituitary was more important for what it failed to show than what it showed. The appearance was that of an exceedingly active adenoma composed of eosinophilic cells but without the slightest evidence of fibrosis or interacinar lymphocytes which might have been expected as a result of irradiation. Thus, we are forced to the conclusion, from both clinical and pathological evidence, that the roentgen-ray therapy given in this case was woefully inadequate. One wonders whether this patient would have been spared much of the acromegalic disfigurement, the complication of diabetes mellitus and the thymic death if he had agreed to submit to subtotal hypophysectomy fairly early in the course of his disease.

*Case 2* (U. C. H. No. 87776). Progressive, outspoken acromegaly in a man, 25 years in duration,

remarkable. He had sustained two broken ribs at the age of 13, which had left him with a permanent deformity of the chest, and a broken nose at the age of 16. He had had scarlet fever in childhood and typhoid fever at the age of 29.

The present illness began at the age of 19 when the patient noted a sudden and rapid increase in height and weight and found that he required increasingly larger hats and gloves (fig. 5, B). His hands became so large that they began to annoy and handicap him in his work. His feet did not grow as rapidly. During the intervening 11 years he had gained 111 lb. (from 145 lb. to 256 lb.). He had noted drowsiness for 3 to 4 years and difficulty in chewing due to increasing prognathism with consequent malocclusion for 2 or 3 years. Libido and potentia had not been impaired. He complained of difficulty in breathing through his nose, of dyspnea on exertion, but he had no palpitation or edema. He had an excellent appetite and a special fondness for carbohydrates. Constipation and an occasional "gas attack" were his only gastrointestinal complaints. Shortly before admission he experienced increased frequency of micturition without polydipsia. Perspiration was profuse. He had had right frontal head-

aches of a sharp, shooting nature for about a year but no visual disturbances, vertigo, dizziness, convulsions or paralysis. When he held his right forearm and hand in the horizontal position, paresthesia occurred which could, however, be relieved immediately by dropping the arm

and showed considerable acne. There were sebaceous warts on the shoulders. The nose was extremely large, the skin and subcutaneous tissues were thickened and the naso labial folds were striking. The nasal septum deviated to the right so that much of the breathing space was



Fig 5 Case 2 A, B, C, ages 16, 20, and 26; D, 39 years; E, F, age 45 years, after death. D, enlargement of nose, frontal bosses and increasing prognathism

E, F, age 45 years, after death. E, F, age 45 years, after death.

His most recent complaint, of one month's duration, was impairment of hearing.

The patient was large and obese. He had a protruding, deformed chest, slight dorsal kyphosis, a prominent abdomen and long arms. The hands were so immense that he could not obtain sufficiently large gloves (fig. 6, A). The height was 74 in (188.0 cm) and weight was 243 lb (110.4 kg). The head was large and showed prominent frontal bosses and a deeply furrowed brow. The lower jaw was protuberant and massive. The hair on the head was thick and coarse while that of the eyebrows was thin and sparse especially in the lateral halves. The skin was coarse

occluded. The pharynx was edematous and injected, the tonsils were hypertrophied and infected. The gums were boggy and retracted and the teeth showed evidence of much dental work. The tongue was large and meaty. The ears appeared normal, however, the patient could not hear the tick of a watch beyond the distance of 3 or 4 cm on either side (normal distance about 9 cm). The chest was normal except for the bulging of the left anterior wall. The abdomen was normal. The heart was not enlarged, the blood pressure was 120 and 65 mm Hg systolic and diastolic, respectively. The genitalia were normal. The extremities, however, were remarkable. The



chiasm was very wide. The pituitary gland was unrecognizable; it consisted of a shapeless mass of necrotic tumor or abscess. The sphenoid sinus contained much greenish-white purulent material. On the floor of the skull were many exostoses, especially over the anterior and middle fossae where plates of bone protruded into the temporal sulci. The crista Galli was very prominent. The brain weighed 1500 gm. (normal 1360 gm.) The pia arachnoid just behind the optic chiasm under the third ventricle was thickened. Sections through this region showed some petechial hemorrhages into the thalamus and small cystic cavities in the lenticular nuclei. The largest of these was not more than 2 mm. in diameter. Petechial hemorrhages, probably agonal, extended along the brain stem into the medulla. The third ventricle was somewhat dilated, although the lateral ventricles were collapsed, and the aqueduct was patent. The blood vessels appeared normal.

The thorax was well clothed. The ribs were widened, thickened and distorted. The heart was greatly enlarged; it weighed 620 gm. (normal 350 gm.). The ventricular walls were considerably hypertrophied, the left measuring 11 mm. and the right 4 mm. The right atrium contained a huge pedunculated thrombus which subtotally occluded the tricuspid orifice and was attached to the valve and chordae tendinae. The left atrium was normal. The coronary vessels were prominent and sclerotic. Atheromatous deposit was seen in the atrial surface of the mitral valve and in the aorta just above the aortic valve. The endocardium seemed to be somewhat thickened and opaque. No valvular lesions or areas of myocardial softening were seen. The pleura was smooth, moist and glistening. The left lung showed extensive bronchopneumonia throughout the lower lobe. Firm areas of consolidation were found in the right lower and the middle lobes. The mediastinal and tracheo-bronchial nodes were enlarged and anthracotic. Remnants of thymic tissue were seen in the superior mediastinum. The thyroid was enlarged, weighing 90 gm. (normal 45 gm.). It contained more colloid than normal and a few small colloid-containing areas were distinctly encapsulated. Two parathyroids were identified.

The stomach and intestines were greatly distended with gas. The peritoneum was smooth, moist and glistening. No free fluid was seen. The appendix was normal. The spleen was greatly enlarged and congested. It was septic in type. The capsule was dull and thickened in places over apparent infarcts. The pulp was soft and easily scraped away with a knife. The liver was enormous, extending over a hand's breadth below the costal margin. It weighed 6200 gm. (the largest liver previously recorded weighed 5900 gm. and normal weight is given as 1500 gm.). The cut surface showed passive congestion with nutmeg appearance. On the inferior surface of the left lobe was a sharply demarcated lighter area which extended into the substance of the liver. The gall bladder contained thin, bloody bile. Its lining appeared acutely inflamed and hemorrhagic. The pancreas showed advanced postmortem softening. The adrenals were enlarged; one contained an adenomatous area about 8 mm. in diameter. The right kidney was about two times normal size; it weighed 460 gm. (normal 300 gm.). The capsule stripped easily, leaving a surface flea-bitten in appearance. The cut surface showed marked swelling. The cortex was thickened and the pyramids were deeply congested. The pelvis

showed many petechial hemorrhages. The left kidney was similar; it weighed 450 gm. The ureters and bladder were normal. The testes were soft but of normal size. The prostate was normal.

*Microscopic findings.* Dr. C. L. Connor made the pathological examination of the tissues after they had been fixed in formalin for a long time. Special stains could not be used, but the findings which are given were recognized without difficulty.

The heart showed large, probably hypertrophic muscle fibers. In many places the muscle had degenerated into collagenous material which had formed scars throughout the myocardium. A section of the coronary artery showed more than 50 per cent occlusion by atheromatous deposits and fibroblastic proliferation into the intima. There was no considerable infarction but the condition resembled the so-called fibrous myocarditis of arteriosclerosis.

Section of the lungs showed a marked infiltration with polymorphonuclear cells into alveoli, bronchi and bronchioles. This part of the lung was aerated in only a few rounded spaces. The condition was an example of severe acute bronchopneumonia.

In the liver patches of fat in more than moderate amount were scattered sometimes around a central vein and sometimes nearer the portal areas. Fibrous tissue was slightly but definitely increased around the lobules, in some places almost completely encircling them. There was some reduplication of the bile ducts in the portal areas with the formation of double cords of cells such as is seen in cirrhosis. No glycogen was present.

Considerable swelling and postmortem degeneration of the epithelium had taken place in the tubules of the kidneys. Some fatty infiltration was seen in the cells of the convoluted tubules. The glomeruli were large. There was slight thickening of Bowman's capsule which may have been due to the prolonged fixation. A similar collagen swelling of the interstitial tissues did not seem to be antemortem edema. The wall of blood vessels was somewhat thickened but showed only a minimal amount of proliferation of the intima. Except for the increase in size and for the lipid deposits in the convoluted tubules, the kidneys appeared normal. No profound change from the normal was found in the testes. Mitotic figures were present in the cells of the seminiferous tubules. Cells of Leydig could be seen in small numbers in the interstitial tissue. These did not appear to be increased or decreased in number or structure.

The three parts of the pituitary gland could be identified although not all of the anterior lobe was in the section. There was no capsule around the gland and an unknown amount of tissue had been lost. What remained of the anterior lobe apparently was composed of one type of cell only which had stainable cytoplasm and was of brick-red color; these apparently were eosinophilic cells which contained granules. The fact that the cytoplasm stains at all may be considered an eosinophilic characteristic. No basophils were found. Very few cells with non-staining cytoplasm were seen (fig. 9). The thyroid contained more colloid than normal. The alveoli were generally larger but groups of smaller alveoli were present. In these, as well as in the larger ones, the cells were not flat but low cuboidal in shape. Many of the lining cells had sloughed away because of postmortem changes. Histologically, the gland

appeared to be simply hypertrophied. However, it showed more than the normal amount of connective tissue and slight infiltration with lymphocytes. The parathyroid glands contained the usual two types of cells, the chief cells being much more numerous than the eosinophils. They looked like normal glands except for their increase in size.

The adrenals were distorted apparently because of an overgrowth of cortical cells since the distortion was more than can be accounted for by mechanical postmortem damage. As in hyperplastic glands, the three layers of cortex were not distinct. There had been numerous localized areas of hyperplasia, some partly encapsulated and some completely encapsulated which formed so-called adenomata. At the same time some thickening of the capsule had occurred with an increase of connective tissue between cells and groups of cells in the outer cortical zone. Deeper in the cortex some islands of connective tissue with processes ramifying through the tissue were observed. These fibrotic changes no doubt represent cortical atrophy following hyperplasia and may be considered an involutionary process even though the gland was hyperplastic. It probably had been more hyperplastic at one time.

The thymus tissue was much more abundant than normal in a person 45 years of age. The mass of fat which included the thymus measured about  $4 \times 3 \times 2$  cm. A large portion of this mass was thymus tissue. It was cellular. In some parts the cortex and medulla could be distinguished. The Hassall's corpuscles were about as far apart as they would be in the thymus of a child, many were present and a few of them were calcified. The condition evidently was due either to lack of normal involution or to hyperplasia.

No important changes were observed in the brain. The cortical tissue around blood vessels was somewhat degenerated. The cysts in the basal nuclei were lined with ependyma and presumably were diverticula from the ventricles.

Pathological diagnoses were eosinophilic adenoma (degenerated) of the pituitary with marked acromegaly, marked visceromegaly, simple hypertrophy of the thyroid and parathyroid glands, and hyperplasia of the thymus and adrenals, coronary sclerosis; purulent sphenoiditis; and terminal bronchopneumonia.

### Summary

In this case the unimpeded progress of acromegalic changes over a period of 26 years is recorded. The disease first manifested itself at the age of 19 with a sudden spurt of growth. When the patient died at the age of 45, he presented an advanced picture of the hideous and grotesque changes which may occur under the influence of an excessive amount of growth hormone.

Except for the urinary findings suggestive of nephritis, the condition was relatively uncomplicated. Headache and visual impairment were minimal and diabetes never developed as far as we know. We did not see the patient during the last 5 years of his life. Because, and only because, of the absence of complications, the condition was allowed to progress for 26

years. The sole therapy given was by roentgen ray, approximately 2100 roentgens in four exposures in 1923. The sudden onset of intractable headache shortly before death may have been caused by an exacerbation of growth of the pituitary adenoma or it may have been related to the purulent infection found in the sphenoid sinus at autopsy. The immediate cause of death was terminal bronchopneumonia.

The advanced degree of visceromegaly found at autopsy is particularly noteworthy. The liver was the



Fig 9 EOSINOPHILIC ADENOMA OF HYPOPHYSIS. Note closely packed cellular structure.  $\times 95$ .

largest which has ever been described in acromegaly (6300 gm). The largest previously reported, by Dallemagne, weighed 5900 gm.

Case 3 (C. H. No. 57403). Post-menopausal onset of acromegaly in a woman, complicated by latent syphilis, arteriosclerosis, hypertension, diabetes mellitus, multiple adenomata of the thyroid, retinal detachment, breast tumor, and pseudo-tubercles. Treatment consisted of pituitary irradiation in inadequate dosage. Death occurred at age 58 from degeneration and hemorrhage of the eosinophilic adenoma of the pituitary into the sphenoid sinus and the pharynx.

A widow, 56 years of age, came to the Out-Patient Department of the Hospital for Women and Children on August 22, 1934, complaining that for 4 years since her menopause, she had had increasing difficulty in locomotion associated with pain and stiffness in the knees and increasing unsteadiness of gait. She had to watch where she put her feet, could not gauge distances and was continually bumping into objects. She often staggered and frequently she fell. Vision was failing steadily, especially in the right

eye which was hemianopic. During the same interval there had been a great change in her appearance which was manifested by progressive enlargement of chin, tongue, nose, hands and feet. She neither suffered from headaches nor was she subject to respiratory infections. She had had palpitation of the heart as well as edema of the ankles for

narrow. The right pupil was smaller than the left, irregular and fixed to light although it reacted consensually. The left pupil reacted normally. The retina appeared to be detached from the temporal portion of the right eyeball. The left disc was somewhat blurred. The visual fields, determined by perimetry with a 5 mm. test object, were

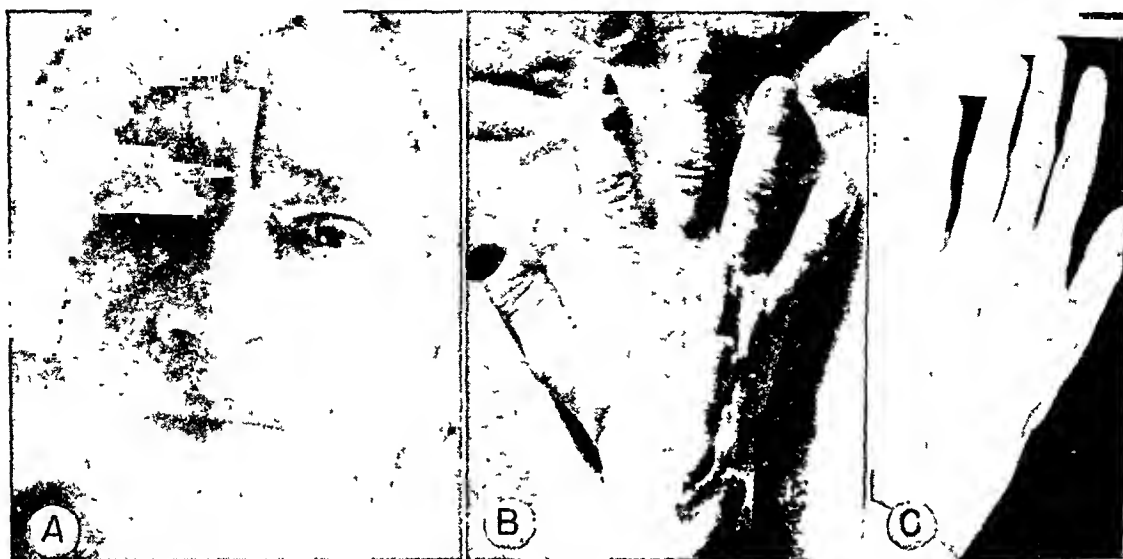


Fig. 10. Case 3. A, age 53 years. Note vertical furrowing and thickening of forehead, marked puffiness around eyes, narrow lid slits, thickened nose and lips. B, note wide wrists and fingers, thickened terminal phalanges, and thickened hypertrophied blood vessels. C, normal adult male hand for comparison.

4 years. She complained of much flatulence and increasing constipation. Nocturia had occurred 2 or 3 times nightly for about 4 years. She had polyuria but no polydipsia. She was always warm, perspired profusely and tired easily. She did not use any alcohol, tobacco or drugs, but drank about 5 cups of coffee and tea daily. The appetite was very good. The maximum weight of 205 lb. was attained at the onset of the illness. About 2 years before the presenting date she had been told that she had diabetes; on a special diet, to which she had adhered only for a short time, she had lost about 35 lb.

The patient was married at the age of 15. Her husband met an accidental death 14 years later. Of 8 pregnancies, 2 terminated in spontaneous abortions. Three children died in infancy. The three living children were 40, 34 and 29 years of age, respectively. The daughter aged 40 had syphilis which may have been congenital. At the age of 54 years the patient had had a moderately severe attack of broncho-pneumonia. Menstruation had begun at the age of 13, periods had occurred every 28 days, had lasted for 5 to 6 days and had been characterized by profuse flow. The menopause was complete at 52 years of age.

The patient presented a typically acromegalic appearance. She had large coarse features, deeply furrowed brow, protruding mandible, prominent frontal bosses, hypertrophic nose and large, spade-like hands (fig. 10, A and 10, B). The height was 62.5 in. and the weight 170 lb. The skin was thick, dry and coarse. She had several pedunculated fibromata on the neck, a large one on the inner aspect of the right thigh and one on the dorsum of the left foot. The eyelids were puffy and the eye slits

normal save for a large nasal defect on the right which may have been due to the retinal detachment. Except for hypertrophy, the nose was normal. The lips were thick and the lower jaw was prognathic. The teeth in the lower jaw were spaced widely and in poor condition; marked periodontitis was present. The upper jaw was edentulous. The tongue was very large and was traversed by a deep midline fissure. The nasopharynx was slightly injected. The tonsils were small and cryptic. The submaxillary, axillary, inguinal and epitrochlear lymph nodes were enlarged. The thyroid was nodular and considerably enlarged. The thorax was barrel-shaped; the sternum was thickened and protruding. The breasts were soft and full but showed no masses or tenderness; the nipples were inverted. The lungs were normal by percussion and auscultation. The heart was considerably enlarged; the point of maximum impulse was in the 6th interspace at the anterior axillary line. A systolic murmur was heard over the entire precordium; it was loudest over the aortic and mitral areas. The systolic blood pressure was 180, the diastolic, 100 mm. Hg. The rounded edge of the liver was palpated about 4 cm. below the costal margin. The hands were large and spade-like. The thickening involved especially the terminal phalanges. The feet were broad and thick. The ankles showed slight pitting edema. The veins and arteries of the upper and lower extremities were hypertrophied and tortuous. Considerable cervicodorsal kyphosis and moderate lumbar lordosis with accompanying limitation of motion were observed. The vaginal outlet was relaxed. A pea-sized fibroma, similar to the fibromata of the skin, was found just inside the introitus.

A considerable amount of yellow discharge was noted. Advanced senile vaginitis was evidenced by adhesions of the vault which obliterated the fornices. The uterus was small, anteriorly situated and freely movable. The adnexae were normal.

The patient's gait was markedly ataxic, she put down her feet in an unsteady manner. The Romberg sign was positive, the patient staggered in all directions. The muscles showed no weakness, atrophy or fibrillation. All movements were performed sluggishly. Taste and smell were normal. There was slight impairment of sensation in the right extremities. The tendon reflexes were equal and active. Clonus and the Babinski sign were absent. Position sense was intact. The ataxia was confined to the lower extremities, the finger-to nose test was well done whereas the heel-to-knee test was poorly done.

The significant observations made by laboratory examination were as follows. The urine, examined on Aug 28, 1934, showed a faint trace of albumin, no sugar, many calcium oxalate crystals, numerous white blood cells and 4 to 5 red blood cells per high dry field. Two weeks later 3+ sugar was found in the urine. The blood count showed Hb 97 per cent (Sahli), RBC 5,300,000, WBC 6000, with polymorphonuclear leucocytes 60 per cent, lymphocytes 39 per cent and transitional 1 per cent. Fasting blood sugar was 296.2 mg per cent. The blood Wassermann reaction was 3+ in three dilutions (Kolmer). BMR was +22 per cent. By electrocardiographic examination of the heart, the rate was 72, the rhythm was regular and of normal sinus origin. The PR interval was 0.16 and the QRS was 0.08 seconds. The P waves were moderately broad and notched and there was evidence of left preponderance consistent with a hypertensive heart.

Stereoroentgenographs of the skull showed that the calvarium was thick and the bony texture was coarse and dense. The sella turcica was enlarged but the floor and the clinoids were intact. The pineal body was densely calcified but not noticeably displaced. The frontal sinuses were strikingly enlarged (fig. 11). Roentgenograms of the hands showed thickening of the bones with characteristic tufting of all terminal phalanges. The knee joints showed rather extensive hypertrophic changes, but no evidence of a destructive lesion. Fluoroscopic examination of the chest revealed a rounded shadow above the arch of the aorta which suggested a substernal extension of the thyroid. The arch of the aorta was sclerotic and wide in the antero-posterior view, partly due to rotation. The heart appeared hypertrophied especially in the antero-posterior diameter.

On the basis of the physical findings the following diagnoses were made: pituitary tumor with acromegaly, diabetes mellitus, latent syphilis, arteriosclerosis with hypertension and cardiac hypertrophy, multiple adenomata of the thyroid, retinal detachment of the right eye, multiple fibromata, varicosities, senile vaginitis, and chronic hypertrophic arthritis. Most of the complications of acromegaly as well as a few extraneous conditions were evident in this case.

Treatment of this patient was difficult because of her failure to cooperate. It consisted of dietary management of the diabetes and control of the syphilis by administration of bismuth salicylate intramuscularly and potassium iodide

orally. Since the patient did not adhere to the diet, the urine never was consistently free of sugar. In February, 1935, following a severe acute upper respiratory infection, the patient was hospitalized for control of diabetes. A glucose tolerance test gave the following results in mg per cent: fasting blood sugar, 234, at  $\frac{1}{2}$  hr, 284, 1 hr, 332, 2 hr, 346, and 3 hr, 206. The quantitative urinary sugar was 8.6 gm or 3.8 per cent. The blood cholesterol was 146.4 mg per cent, the BMR was +36 per cent. Lumbar puncture yielded a clear, colorless fluid under a pressure of 210 mm of water, sugar of 110 mg per cent, a cell count of 10 with 50 per cent polymorphonuclears and 50 per cent lymphocytes, negative Wassermann.

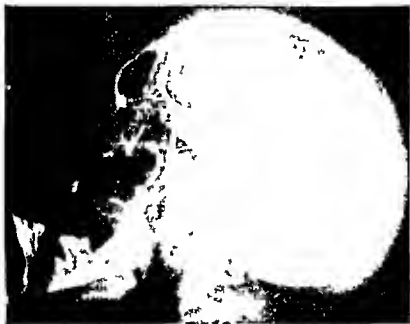


Fig. 11. ROENTGENOGRAM OF SKULL OF case 3. Note thickened calvarium, huge frontal sinuses, prognathism and enlarged sella turcica.

mann and Pandey reactions, a slightly positive Nonne and a gold curve of 0111211000.

After a week's hospitalization the patient was discharged with sugar free urine, on a diet which consisted of carbohydrate, 100 gm., protein, 65 gm., and fat, 100 gm. (a total of 1566 calories), without insulin. Three months later the urine still was sugar-free, the fasting blood sugar was 190.4 mg per cent. Since the diabetes and syphilis were under control, pituitary irradiation was begun. After 3 roentgen ray treatments to the region of the hypophysis, the patient volunteered the information that her shoes seemed large and that her hands were less puffy than previously. The adenoma of the thyroid was definitely smaller, but this may have been an iodide effect. Roentgen ray therapy was continued until a total of 800 r had been given to each side. The last treatment was given on August 20, 1935.<sup>4</sup>

Four months later, in December, 1935, the patient had a severe upper respiratory infection which persisted for 11 days. Following this illness a very hard, painless mass about the size of an egg appeared just below the nipple of the right breast. It was attached to the overlying reddened skin. A large lymph node was palpable in the right axilla. The left nipple was inverted and a small firm lump was observed beneath and medial to it. Both nodules were opaque to transillumination. The condition suggested carcinoma. Surgical exploration was to be done.

<sup>4</sup> For details of roentgen ray dosage see Addenda, synopsis of roentgen ray therapy, case 3.

after a few days of treatment with hot compresses to allow the inflammatory reaction to subside. The patient failed to return until 9 days later at which time the mass was smaller and more rubbery. One month later the mass had disappeared and the diagnosis was revised to inflammatory mastitis.

Early in 1936 the patient again was hospitalized for control of diabetes. The fasting blood sugar was 285.6 mg. per cent and the cholesterol 303 mg. per cent. When she was dismissed on Feb. 29, 1936, the urine sugar-free, on a diet consisting of carbohydrate, 110 gm.; protein, 70 gm.; and fat, 100 gm. (a total of 1620 calories) and insulin 12.0-12 U, the fasting blood sugar had dropped to 153.8 mg. per cent and the blood cholesterol to 250.5 mg. per cent. From this time on the patient became completely discouraged and unco-operative. Whether the necessity for injections of insulin was responsible for her attitude is difficult to say. Her condition became steadily worse. Finally, on Sept. 30, 1936, she entered the San Francisco Hospital in coma with temperature of 104.6°F. For several weeks before entry she had vomited and had suffered from severe headache. She was said to have lost the lateral field of vision in the left eye. On examination the left pupil was dilated and failed to react to light. A choked disc was observed in the left fundus. She had bleeding from the left side of the pharynx. The blood pressure was 240 and 100 mm. Hg systolic and diastolic, respectively. The knee jerk reflexes were diminished. A blood count showed: Hb. 98 per cent, R.B.C. 6,000,000, W.B.C. 12,200 and a normal differential count. The spinal fluid contained 27,000 cells of which 45 per cent were red blood cells and the remainder were polymorphonuclear cells. The patient died on Oct. 1, 1936, without having regained consciousness.

### Autopsy

*Gross findings.* The body was that of an obese, grey haired, acromegalic female about 50 years of age. Distribution of the hair was normal. The right pupil measured about 3 mm. and the left about 5 mm. in diameter. The nasal septum was intact. The upper jaw was edentulous; several teeth were missing from the lower jaw; those remaining were fairly well preserved. The tongue was large. There was a blood clot in the pharynx on the left side but no bleeding point was seen. A movable mass about 3 cm. in diameter which was not attached to the skin was seen under the ramus of the jaw on the right. The trachea was in the midline. The breasts were small and showed inverted nipples. The chest and abdomen were not remarkable. The genitalia appeared normal. The lower extremities were relatively normal but the upper ones were disproportionately long, extending to the middle of the thigh. The hands were exceedingly large with huge phalangeal joints and clubbed fingers. There were several papillary skin lesions over the body, some extending as far out as 2 cm.

The scalp stripped from the skull with ease. The calvarium was thickened, measuring 1 cm. at one point but the bone was rather soft and could be sawed with ease. The meninges were normal. The brain weighed 1250 gm. (normal 1360 gm.). Its surface appeared normal. No palpable tumors were found within the brain substance. The anterior and posterior clinoid processes were eroded

away. The sella turcica was deepened and filled with the enlarged pituitary gland which had penetrated through the floor into the sphenoid sinus and at one point into the pharynx. At this point bleeding was observed. The pituitary was approximately 4 times normal size and weighed 12 gm. It was soft, congested and had no distinct form. The thyroid was enlarged and congested. The left lobe weighed 45 gm. and the right 55 gm. (normal total weight 45 gm.).

The pleural cavity contained no free fluid but adhesions were seen between the apex of the left lung and the rib cage. The left lung was subcrepitant throughout. The bronchi appeared normal. The pulmonary vein contained no antemortem clot. The lymph nodes were small and anthracotic. On cut section the lung was somewhat congested and the apex was slightly scarred. No areas of consolidation were seen. The right lung was similar to the left.

The pericardial cavity was obliterated by dense, firm adhesions. The heart with adherent pericardium weighed 525 gm. (normal 250 gm.). The right ventricle measured 4 mm. and the left 5 mm. in thickness. The endocardium was smooth throughout. The valves were normal. The auricles contained no antemortem clots. The coronary arteries showed considerable arteriosclerosis but no obliteration or narrowing.

The abdominal cavity contained no free fluid. The serosal surfaces were smooth and shiny. The appendix was bound to the parietal wall by dense, firm adhesions. One adhesion was observed between the gall bladder and the large bowel. The diaphragm extended to the 5th interspace on the right and to the 5th rib on the left. The liver did not extend below the costal margin. It measured 30 × 25 × 8 cm. and weighed 2350 gm. (normal 1500 gm.). Its surface was smooth except for a plaque of scar tissue 3 × 4 cm. in the left lobe. The parenchyma under the scar tissue was dense and firm and cut with resistance while that of the liver in general was rather pale and showed fatty trabeculations. The gall bladder contained 30 cc. of tan-colored bile. The biliary passages were patent. The spleen weighed 460 gm. (normal 200 gm.) and measured 18 × 9 × 3 cm. Its surface was smooth and on cut section appeared congested. The left kidney was pale, weighed 245 gm. (normal 300 gm.) and stripped with great difficulty. The cortex was 8 mm. thick. It contained a normal amount of perirenal fat. The renal pelvis was normal. The right kidney weighed 240 gm. and resembled the left. The adrenals appeared normal in size and shape. The left weighed 5 gm. and the right 15 gm. The pancreas was normal. The aorta was sclerotic throughout its entire length. The spinal cord in the lumbar region appeared normal. The small and large bowels contained dark, bloody material. The vaginal wall was thickened throughout, with small plaques of dense fibrous tissue. The cervix was atrophic and the os was patent. The uterus was normal in thickness but contained two papillomata in the mucosa. The fallopian tubes were apparently normal. The ovaries were approximately normal in size but were firm and almost stony in consistency.

*Microscopic findings.* In the brain numerous calcareous bodies were observed in the choroid plexus of the left posterior horn of the ventricle. The meninges at the base

of the brain were congested and contained moderate numbers of polymorphonuclear leucocytes. The hypothalamus contained numerous amyloaceous bodies. The tissue was loose and there were a few round cells about several of the vessels. The pituitary (fig 12) was replaced largely by hemorrhagic necrotic debris and great numbers of polymorphonuclear leucocytes. The acini which remained intact stained pink with hematoxylin and eosin and were widely separated by edema and hemorrhage as well as infiltrated by red blood cells and polymorphonuclear leucocytes. The overlying meninges were thickened with fibrous tissue and also were heavily infiltrated with the same type of cells. The submaxillary mass showed increased fibrous tissue reaction about lymphoid elements. The polypoid mass in the skin was covered by normal epithelium and was composed of masses of hyalinized fibrous tissue. The acini of the thyroid were lined with cuboidal epithelium and filled with pink staining colloid. An increased amount of interlobar connective tissue was noted indicating involution perhaps of a previous hyperplasia.

The fibrous tissue strands between the muscle fibers of the heart were moderately increased. The pericardium showed fibrous tissue thickening. There was a generous sprinkling of round cells and polymorphonuclear leucocytes among the muscle bundles. A large calcareous plaque was seen in the intima of the aorta. Slight scarring about the vasa vasorum and a few round cells were present. The alveolar walls of the lungs were congested and the alveoli contained debris and occasional red blood cells and leucocytes. The septae contained fibrous tissue.

The liver showed marked increase in perilobular connective tissue of the cells and contained increased fat. The wall of the gall bladder was edematous and showed fibrous tissue thickening. Small collections of round cells were present in the mucosa the villi of which were thickened and adherent to one another. A large artery in the wall contained collections of round cells about the vasa vasorum. The pulp of the spleen was congested and infiltrated with polymorphonuclear leucocytes. The vessels of the pancreas were congested, only a few small islets were present. The kidneys contained small collections of round cells under the capsule and about some of the congested blood vessels. The glomeruli were large but otherwise normal. An occasional hyaline cast was seen in the tubules. The adrenals were normal.

The breasts showed ducts which appeared to be dilated. One duct was filled with an intracanalicular mass of fibrous tissue and had no lining epithelium. Large foci of round cells were seen about the ducts and acini. No follicles of germinal epithelium were present in the ovaries. The ovarian tissue was replaced by corpora albicantia and fibrous tissue. The uterus showed atrophic endometrial glands some of which had become cystic and were lined by low columnar epithelium and were filled with pink staining debris. The uterine muscle was fibrotic. The salpinx showed a slight increase in the connective tissue of the fimbriae. Underlying the atrophic epithelium of the vagina were numerous round cells. The spinal cord was riddled with small amyloaceous bodies. The cells of the dorsal column and anterior horn were normal. The meningeal vessels were congested but showed no inflammatory change.

The pathological diagnoses were eosinophilic adenoma of the pituitary with perforation of the sphenoid sinus and hemorrhage into the pharynx, acromegaly, acute basilar meningitis, simple nodular goiter, chronic adhesive pericarditis, generalized atherosclerosis with cardiac hypertrophy, multiple polypi of the uterus, multiple fibromata of the skin, chronic cystic mastitis, intracanalicular fibroma of the breast, chronic cholecystitis, healed apical pulmonary tuberculosis, and chronic submaxillary lymphadenitis.

### Summary

The onset of acromegaly in this case occurred at the age of 52 years, following the menopause. The

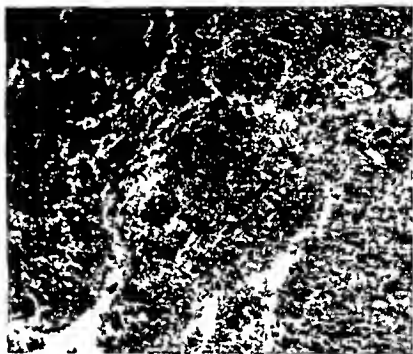


Fig 12 Case 3 EOSINOPHILIC ADENOMA OF THE HYPOPHYSIS. Note degeneration and areas of hemorrhage and edema.  $\times 120$

duration of the disease was 6 years. Death was due to hemorrhagic necrosis of the pituitary adenoma with extension through the sellar floor into the sphenoid sinus, and hemorrhage into the pharynx. The symptoms were acral enlargement, difficulties with locomotion, failing vision, polyphagia, polyuria and profuse perspiration. Headache appeared terminally.

The complications were numerous and confusing. Diabetes appeared early in the course of the disease, having been diagnosed 2 years after the onset. It was poorly controlled. The visual field defect, which is so characteristic of pituitary tumors, was due in this case to a retinal detachment. This complication has been reported only once before in acromegaly in a recent article by Flaum and Ralli (9). The presenting complaint of locomotive difficulties of an ataxic nature and the positive serology were suggestive of tabes. Closer study showed that it was undoubtedly a pseudo tabes which has been described previously in conjunction with acromegaly. The cardiac symptoms and findings were difficult to evaluate during life. How much of the symptomatology was due to arteriosclerosis and hypertension, how much to the visceromegaly which is an integral part of acromegaly, how



much to the mildly toxic adenomata of the thyroid, and how much to syphilis, was difficult to establish. The syphilis probably was latent and of long standing. Atkinson (6) in his searching compilation reported the incidence of syphilis in acromegaly as about 10 per cent. Since the same incidence occurs in the general population, we may conclude that the association of syphilis with acromegaly in this case was purely coincidental. Another complication was the mass in the left breast which made its appearance not long after pituitary irradiation was begun. It was at first considered to be carcinomatous but eventually proved to be an intracanalicular fibroma associated with chronic cystic mastitis. Therapy was difficult to carry out because of the poor cooperation of the patient. It consisted of dietary control with and without insulin for the diabetes, bismuth salicylate administered intramuscularly and potassium iodide orally for the syphilis, and an inadequate amount of irradiation (consisting of 1600 roentgens) to the hypophysis which caused prompt although transient improvement.

*Case 4 (U. C. H. No. 15477).* Acromegaly of about 19 years' duration in a woman, with early and persistent amenorrhea, blindness and diabetes mellitus, treated by transphenoidal partial hypophysectomy and inadequate pituitary irradiation which resulted in partial restoration of vision but had no effect on amenorrhea or diabetes. Xanthoma diabeticorum was a complication. Death occurred at age 43 by suicide.

The patient, a single woman 33 years of age, was born in Minnesota of American parents of French-Norwegian extraction. She first came to the Out-Patient Department of the University of California Hospital on Oct. 5, 1928, complaining of general weakness of 3 to 4 months' duration. The family history was non-contributory. The past history was negative except that she had had small-pox at the age of 10, pertussis as a young child and again at the age of 15, and measles at the age of 20. Catamemia, which had begun at the age of 13, had been normal. Regular periods occurred at 28-day intervals and lasted 4 days. The amount of flow was normal.

A resumé of the symptoms pertaining to the patient's complaint revealed the following sequence of events. Menstrual irregularity began at 24 years of age and progressed to complete amenorrhea at the age of 25. Simultaneously right-sided facial 'neuralgia' occurred at about monthly intervals. Size of hands and feet increased at the age of 30; the patient's attention was first attracted to it because of increasing difficulty in playing the violin, but she attributed the trouble to heavy work. Vision began to fail, at first in the right eye and later in the left eye (an optician had trouble in finding a spectacle frame wide enough to bridge her face). In spite of these difficulties the patient considered herself well until 3 to 4 months prior to the presenting date at which time she was forced to stop work as a power machine operator because of extreme nervousness, irritability and weakness. Sleep was disturbed by severe noctidrosis. The appetite,

which had always been good, had become excessive and she had gained 37 lb. in 4 years (112 to 149 lb.) She admitted a slight increase in thirst but she had not had polyuria. She had suffered from constipation, chronic nasal catarrh and tinnitus aurium for many years. For 2 to 3 months she had experienced some headache.

The patient's height was 64 in. (162.2 cm.) and the weight 149.5 lb. (68 kg.). She was typically acromegalic in appearance (fig. 13, E) with marked prognathism of the lower jaw, prominent malar eminences, wide nose and full lips. The brow was low and broad with heavy, wrinkled folds and prominent frontal bosses. Tenderness was elicited over the right mastoid and the right frontal region. The complexion was swarthy with numerous dark, pigmented spots. The hair was kinky. Despite the patient's purported French-Norwegian ancestry, she was definitely negroid in appearance (fig. 13, B). The eyes were widely separated, the upper lids were puffy and there was a tendency to a nasal brow. Slight exophthalmos was present, the right eye being somewhat more prominent than the left. Intraocular tension was increased. The right pupil was circular, regular and responded sluggishly to light and accommodation. The left pupil also was round and regular in outline but was widely dilated and responded only consensually to light. There was lateral nystagmus both to the right and to the left. The extrinsic muscles responded normally although a suggestive von Graefe sign was present on the left and convergence was poor. Visual acuity on the right was 20/70-2 while with the left eye the patient could barely detect light. The right fundus was normal but the left showed a completely atrophic disc. The fields were limited to nasal vision in the right eye (fig. 14, A). The teeth were widely spaced, the jaws did not approximate properly and oral hygiene was poor. The tongue was huge, being both wide and long. The tonsils were hypertrophied, the right more so than the left. Large submaxillary lymph nodes were palpable bilaterally. The thyroid was smooth, symmetrical and moderately enlarged, without nodules, thrill or bruit. The costal margin was flared. The breasts were moderately well developed. The lungs were normal and the heart was normal save for its slow rate (58 per minute). The blood pressure was 122 and 90 mm. Hg, systolic and diastolic, respectively. The abdomen was normal except for mild tenderness over McBurney's point. The hands were broad with long, flat, wide fingers. The joints were astonishingly supple. The feet were broad. The toes were exceedingly wide. The tendon reflexes were normal. Slight cervicodorsal kyphosis was present. The external genitalia were normal. The hymen was intact. On rectal examination the cervix was palpated posteriorly. The uterus was not palpated clearly but showed no tenderness or abnormal masses.

The urine had a specific gravity of 1.025, no albumin 1+ sugar and negative microscopic findings. The glucose tolerance test gave the following results in mg. per cent: fasting blood sugar, 116;  $\frac{1}{2}$  hr., 206; 1 hr., 217; 2 hr., 206; the urine showed 1+ sugar in the fasting,  $\frac{1}{2}$ -hr. and 1-hr. specimens and 2+ sugar in the 2-hr. specimen. B.M.R. was -4.1 per cent. The blood Wassermann reaction was negative. Roentgenogram of the skull showed marked enlargement of the sella turcica with thinning of the anterior and posterior clinoid processes and depression



Fig 13, A, B, C Case 4 A, age, 24 years, just prior to onset of acromegaly B, age, 33 years, when first seen C, age, 38 years Note startling change in features, especially the nose, lips and forehead, also the pigmentation and darker frizzier hair

of the floor The lower jaw was typically acromegalic (fig 15, A) Roentgenogram of the hands (fig 15, B) and feet showed tufting of the distal phalanges and exostoses of both great toes Bony defects were seen in the terminal phalanges of both thumbs at corresponding points and in the left fifth digit at the proximal interphalangeal joint Roentgenogram of the chest did not reveal cardiomegaly

The diagnoses, made on basis of the physical and laboratory investigations, were pituitary tumor impinging on the optic chiasm and causing blindness on the left and temporal hemianopsia on the right, acromegaly, and diabetes

On Oct 24, 1928, a transphenoidal decompression was performed by Dr Howard Fleming After the sphenoidal sinus had been exposed and the anterior wall removed, a glandular type of tissue extruded A piece about the size of a marble was removed in bits On microscopic section this tissue showed sheets of cells without pattern in a capillary stroma The cells had round vesicular nuclei and faintly staining grey to pinkish-grey cytoplasm without definite membranes No basophils and only a few acidophils were present Although the predominant cells had a non staining cytoplasm, Dr C L Connor, the pathologist, concluded that the tumor probably was an acidophilic adenoma, struma or hyperplasia Recovery from the operation was uneventful The patient was discharged from the hospital on Nov 10, 1928, after having received 4 roentgen ray treatments to the pituitary region, or about 700 r to each side<sup>5</sup> At this time the B M R was -1.5 per cent and the glucose tolerance test gave the following readings in mg per cent fasting blood sugar, 93,  $\frac{1}{2}$  hr, 207, 1 hr, 256, and 2 hr, 210

Three months later the patient's vision was much improved (fig 14, B), the night sweats and headache had disappeared, the hands seemed smaller and the face less thick, suggesting a decrease in the so called acromegalic myxedema However, menstruation had not returned nor had any improvement in diabetes taken place As a matter of

fact, sugar tolerance was depressed further by the complication of a pulmonary abscess which required 5 weeks' hospitalization (May 14, 1929 to June 16, 1929) The patient was discharged cured of the abscess and the urine sugar free, on a diet of carbohydrate, 90 gm, protein, 90

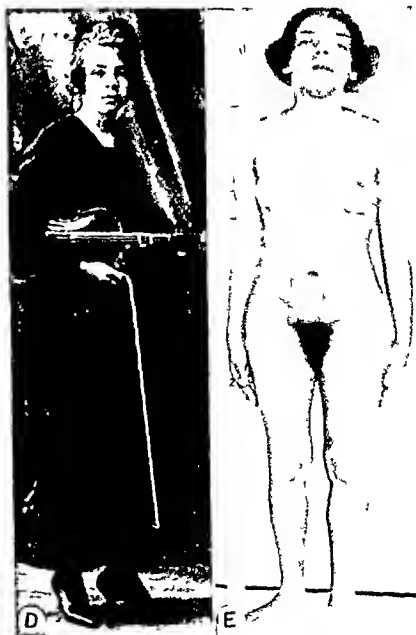


Fig 13, D, E Case 4 D, patient at age of 24, just prior to onset of acromegaly E, age, 33 years, when first seen

<sup>5</sup> For details of roentgen ray dosage see Addenda, synopsis of roentgen ray therapy, case 4



gm.; and fat, 120 gm. (a total of 1800 calories), without insulin. Nevertheless, 3 months later (Sept. 20, 1929) the fasting blood sugar was 333 mg. per cent with an orange reduction of the urine to Benedict's solution. Finally, she was stabilized on a diet consisting of carbohydrate, 90 gm.; protein, 90 gm.; and fat, 100 gm., with insulin 25-10-

was discharged, urine sugar-free, on a diet consisting of carbohydrate, 100 gm.; protein, 60 gm.; and fat, 120 gm., with insulin 25.5-20 u. The B.M.R. at this time was -21.9 per cent.

From 1930 to 1935 the patient got along fairly well. The smooth course was marred only by the occurrence in 1932

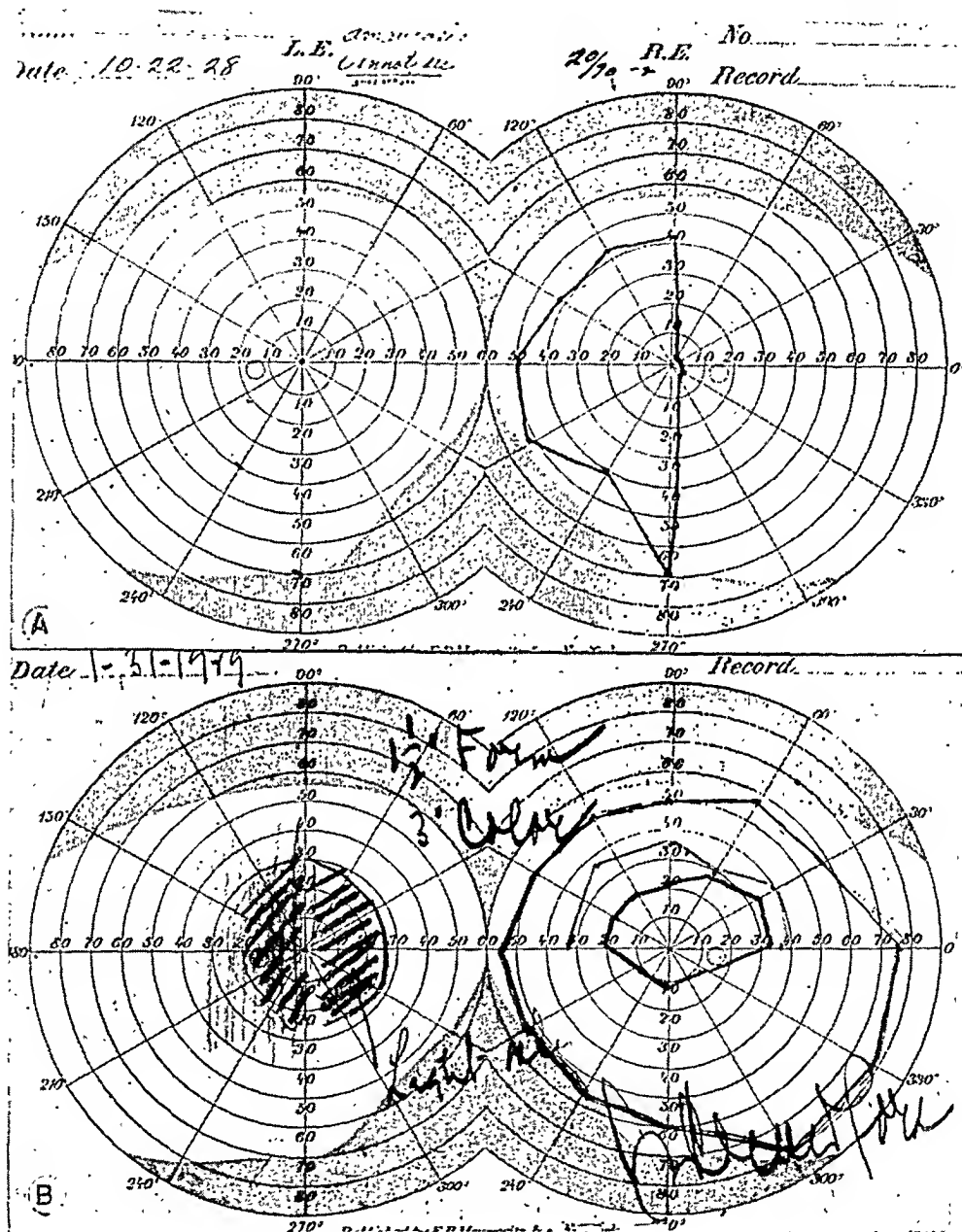


Fig. 14. A. PERIMETRIC CHART OF case 4 at age of 33. Note amaurosis of left eye and hemianopsia of right eye. B, field of vision 3 months after transphenoidal partial hypophysectomy and minimal amount of pituitary irradiation. Note improvement.

15 u. Because of the increasing severity of the diabetes another course of pituitary irradiation was given (about 1750 r). By Dec. 4, 1929, the insulin requirement had increased to 35.25-30 u in spite of the weighed diet. On December 10, the fasting blood sugar was 472 mg. per cent. The patient discontinued taking insulin on Jan. 1, 1930, and failed to return until she was brought to the hospital in diabetic acidosis on March 21. Two weeks later she

of a diffuse disseminated xanthomatosis which lasted for about 6 months. The full details of this complication were reported in 1933 by McGavack and Shepardson (10). The maximum improvement of vision was reached in February, 1934, when the visual acuity was 20/30 in the right and 20/70 in the left (fig. 14 C). In 1931, samples of blood were sent to the laboratory of Dr. Herbert M. Evans for assay of growth hormone; none was found. In 1933 the

patient was for the first time described as a negress

Between 1935 and 1938, although the diabetes was well controlled, the acromegalic signs increased and a slow but progressive diminution in visual acuity of the right eye became apparent. Roentgenograms of the skull showed further enlargement of the sella turcica and tilting of the pos-

is not known since on May 21, 1938, at the age of 43, the patient ended her life by taking poison

### Autopsy

**Gross findings** The autopsy was performed by Dr Jesse Carr, of the Coroner's office. The body was de-

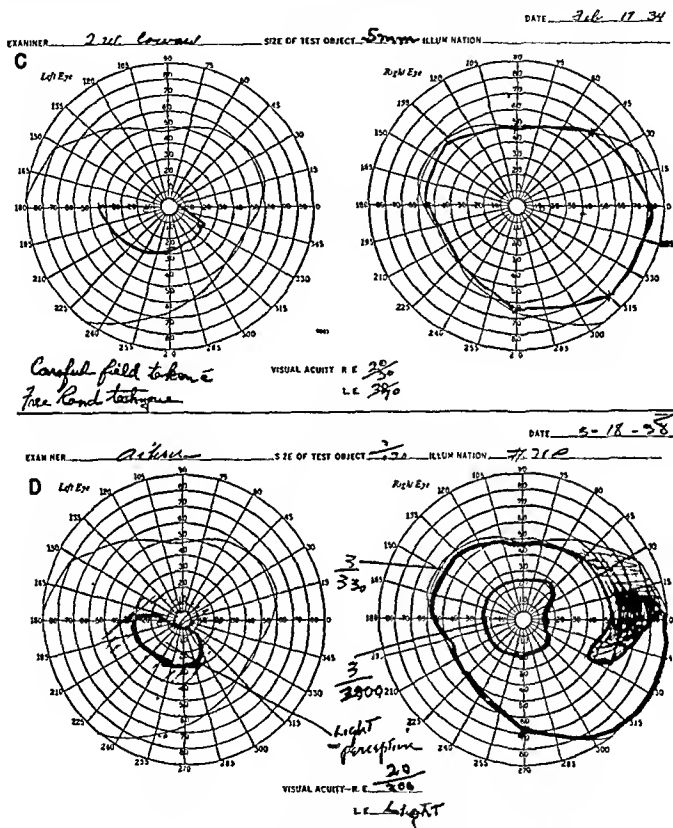


Fig 14 C PERIMETRIC CHART OF case 4 at age of 39. Note maximum improvement in visual fields and acuity D, visual fields 2 months prior to death

terior clinoids. On Jan. 11, 1938, the patient was seen in consultation with Dr Howard Naffziger who advised surgical treatment. This the patient refused because of her mother's illness. By March, 1938, she was suffering from persistent headache and intractable vomiting. Visual acuity had diminished to 20/200 in the right eye while in the left eye she could discern light only (fig. 14, D). Between 21 and May 4, she received almost daily roentgen ray treatments to the hypophyseal region, 850 r to the left side and anterior field and 900 r to the right lateral field, or a total of 2600 r. The effectiveness of these treatments

scribed as that of a negress with black, kinky hair and an old scar on the left side of the chest posteriorly. The lungs showed a few old apical adhesions. The heart presented a few tiny sub-epicardial petechiae. The coronary arteries were extremely sclerotic throughout and in some areas showed 75 per cent occlusion. The cardiac valves and aorta were slightly sclerotic. There was an area of fibrosis, 1 X 5 in. wide, in the posterior wall of the left ventricle. The liver showed moderate passive congestion and fatty replacement. The gall bladder, spleen and pancreas were normal. The kidneys were large, pale and greasy. The

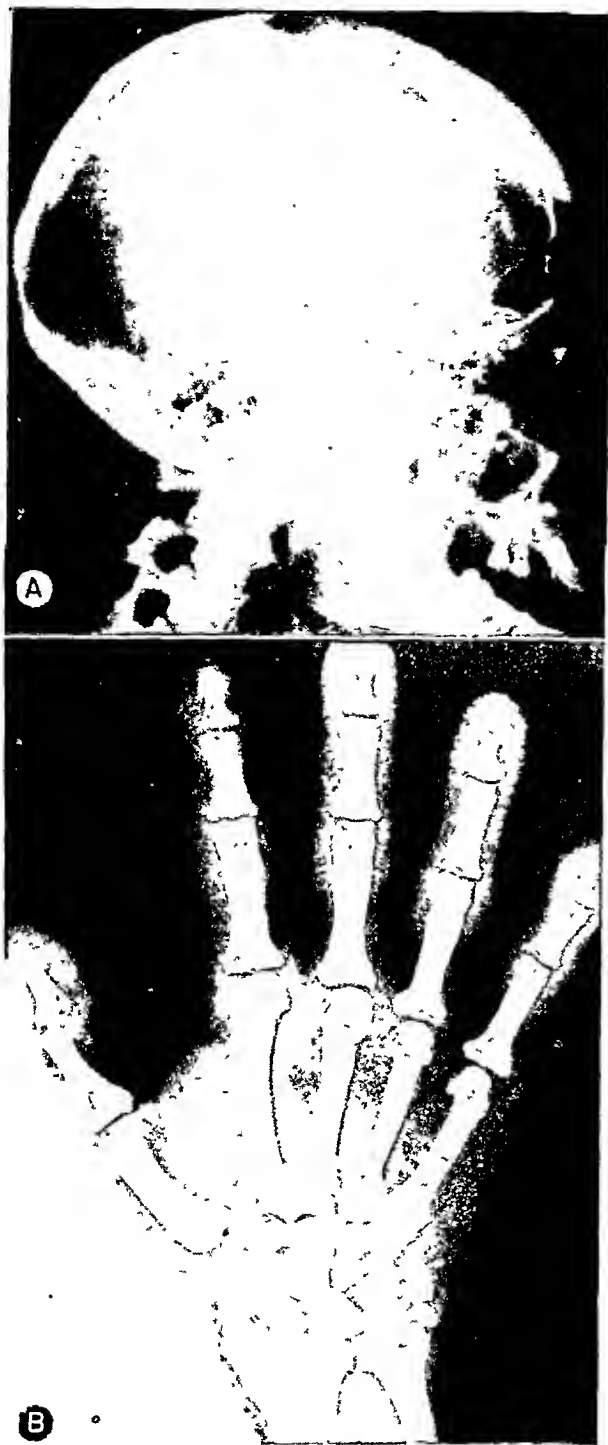


Fig. 15. A. ROENTGENOGRAM OF SKULL OF case 4. Note large sinuses, prognathism and large bulging sella with depressed floor and thinning of anterior and posterior clinoid processes B. ROENTGENOGRAM OF HAND OF case 4. Note characteristic tufting of terminal phalanges and osseous defects in distal phalanx of thumb.

stomach showed many tiny petechial hemorrhages. The appendix was normal. About 3 ft. above the cecum a Meckel's diverticulum 4 in. in length was seen. The intestines contained a yellowish liquid and a few tiny petechial hemorrhages. The uterus was atrophic and the ovaries were small and sclerotic. The scalp and skull were normal. The brain weighed 1500 gm. and measured  $16 \times 15 \times 10$  cm. There was moderate sclerosis at the base and

some edema throughout. The pituitary measured 4 cm. in diameter and was the site of a tremendous overgrowth which had caused great pressure upon the optic chiasm.

*Microscopic findings.* The pituitary gland was edematous. It consisted of heavy masses of small round cells with small nuclei and pink eosinophilic granules. A slight amount of fibrosis was evident (fig. 16). The breasts contained dense hyaline stroma which supported small glands and dilated ducts that were surrounded by diffuse lymphocytic infiltration. The adrenals showed abundant cortical lipid material but had normal cortical zones. There was some brown degeneration in the medulla. The ovaries presented the picture of a dense stroma without evidence of germinal epithelium or follicular development. Two small cysts lined with epithelium were seen.

*The pathological diagnoses* were eosinophilic adenoma of the pituitary gland with acromegaly; advanced coronary sclerosis with subtotal occlusion and myocardial infarction; bilateral apical pleural adhesions; Meckel's diverticulum; sclerosis of the ovaries; atrophy of the uterus; chronic cystic mastitis and atrophy of the breasts.

#### SUMMARY

The acromegaly in this case began at about the age of 24 years with the classical symptom of amenorrhea. The typical skeletal changes were far advanced and the field of vision was seriously impaired (the patient had only nasal vision in one eye) when the patient presented herself at the age of 33. She came mainly because of symptoms referable to diabetes which apparently had been of fairly recent origin. Pronounced pigmentary changes together with the characteristic broadening of the features combined to give this woman of French and Norwegian ancestry a definitely negroid appearance.

A transphenoidal decompression with partial hypophysectomy, followed by relatively small doses of roentgen-ray to the pituitary region, resulted in considerable improvement of vision, in disappearance of headache and night sweats and in diminution of the acromegalic myxedema, but had no effect on the diabetes or amenorrhea. For 6 years (between 1929 and 1935) during which time additional pituitary irradiation to the extent of 1750 r was administered, the progress of the acromegalic changes apparently was held in abeyance. However, the patient's course was complicated by a pulmonary abscess, one bout of diabetic acidosis and a diffusely disseminated xanthomatosis. During the following 3 years, from 1935 to 1938, the diabetes was well controlled but unmistakable signs of a slow but progressive enlargement and increased activity of the pituitary tumor appeared. Surgical treatment was recommended but refused by the patient. Therefore additional pituitary irradiation in the amount of 2600 r was administered. What effect this treatment may have had cannot be postulated since the patient terminated her own life.

Since exitus occurred only 17 days after the last

roentgen ray treatment, this case afforded the rare opportunity of studying the histological effects of roentgen rays on the human pituitary, or at least on an eosinophilic adenoma of the gland. Careful study of the sections showed that although there was evidence of edema and fibrosis, which were not apparent in the sections of the pituitary glands in the preceding cases, the histological changes attributable to roentgen ray therapy were minimal and not indicative of therapeutic effectiveness.

An additional point of interest in this case is the early occurrence of amenorrhea which frequently is found in acromegalic women. This phenomenon is compatible with the presence of completely sclerotic ovaries and with atrophic breasts and uterus.

#### DISCUSSION AND CONCLUSIONS

Certain observations made in these 4 cases of acromegaly stand out in bold relief. All four patients came to an untimely death (at the age of 37, 45, 58 and 43, respectively). In each instance death was caused by the extension or degeneration of the pituitary tumor or by one of the numerous complications of acromegaly. Even the death of suicide may be attributed directly to the disease since life under this handicap was no longer endurable to the patient.

Were these untimely deaths avoidable? If so, how? The very characteristics of the disease, its insidious development, its rarity, its extremely chronic but cyclic course with spontaneous exacerbations and periods of inactivity, and its multiplicity of complications which sometimes overshadow the evidence of the primary disease, all contribute to the difficulty of the problem. How is the status of an acromegalic to be evaluated at any one point in the course of his malady? When is the disease active, when is it quiescent? When does the patient require treatment? When is watchful waiting indicated? If signs of activity are present, what is the treatment of choice?

The dictum heretofore generally accepted was that surgical intervention is warranted only when vision is endangered or when life is threatened by signs of increasing intracranial pressure. These we shall call the neurological considerations. Hypophysectomy for endocrinological reasons alone is rarely done. Roentgen ray therapy is the only alternative treatment. If the tumor is radiosensitive, the response even to moderate dosage, as far as improvement of visual fields and headache are concerned, is likely to be prompt. But the dosage usually is insufficient to arrest the endocrine activity of the tumor. In other instances the tumor, inhibited temporarily by roentgen ray, resumes its pathological activity in the course of time so that further treatment is required. The truth of this observation is demonstrated by the sections of the eosinophilic adenomas of the pituitaries in these

four cases (fig 4, 4, 9, 12 and 16). All four patients had some roentgen ray therapy, the first patient had four courses. Nevertheless, the microscopic picture of 3 of the pituitary adenomas was that of actively functioning tissue. The patient in Case 4 received 2600 r to the pituitary only 3 weeks before death, although there was some evidence of fibrosis, the cytological picture still was that of a fairly active gland.



Fig 16 EOSINOPHILIC ADENOMA of anterior hypophysis of case 4. Irradiation (2600 r) 3 weeks before suicide. Note edema and slight amount of fibrosis.  $\times 85$ .

Besides the neurological findings and the alterations in sella turcica, visual fields and eye grounds, what are the criteria by which the intensity of the endocrine pathologic physiology can be evaluated? The most faithful observations of an acromegalic from month to month or from year to year may fail to impress one with the insidiously progressive changes in features and in the skeleton unless calibrated photographs are taken periodically for comparison. Careful follow up records of head size, shoe and glove size and chest measurements should be made. Dental casts offer a better gauge of mandibular changes and separation of teeth than x ray films. Alterations in the skull and sella turcica should be recorded by repeated roentgenograms at regular intervals. These are the methods of measuring the bony changes. Dare we wait, however, until these changes become measurable? They are irreversible. If we procrastinate we may lose the most favorable opportunity for prophylactic treatment. What are the signs and symptoms of acromegalism?

In our experience, any acromegalic who has an increased basal metabolic rate, who shows lowered



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**The pathological diagnoses** were eosinophilic adenoma of the pituitary gland with acromegaly; advanced coronary sclerosis with subtotal occlusion and myocardial infarction; bilateral apical pleural adhesions; Meckel's diverticulum; sclerosis of the ovaries; atrophy of the uterus; chronic cystic mastitis and atrophy of the breasts.

#### SUMMARY

The acromegaly in this case began at about the age of 24 years with the classical symptom of amenorrhea. The typical skeletal changes were far advanced and the field of vision was seriously impaired (the patient had only nasal vision in one eye) when the patient presented herself at the age of 33. She came mainly because of symptoms referable to diabetes which apparently had been of fairly recent origin. Pronounced pigmentary changes together with the characteristic broadening of the features combined to give this woman of French and Norwegian ancestry a definitely negroid appearance.

A transphenoidal decompression with partial hypophysectomy, followed by relatively small doses of roentgen-ray to the pituitary region, resulted in considerable improvement of vision, in disappearance of headache and night sweats and in diminution of the acromegalic myxedema, but had no effect on the diabetes or amenorrhea. For 6 years (between 1929 and 1935) during which time additional pituitary irradiation to the extent of 1750 r was administered, the progress of the acromegalic changes apparently was held in abeyance. However, the patient's course was complicated by a pulmonary abscess, one bout of diabetic acidosis and a diffusely disseminated xanthomatosis. During the following 3 years, from 1935 to 1938, the diabetes was well controlled but unmistakable signs of a slow but progressive enlargement and increased activity of the pituitary tumor appeared. Surgical treatment was recommended but refused by the patient. Therefore additional pituitary irradiation in the amount of 2600 r was administered. What effect this treatment may have had cannot be postulated since the patient terminated her own life.

Since exitus occurred only 17 days after the last

four cases described here, but we merely wish to point out some of the problems commonly encountered

**Röntgen ray therapy** At the present time pituitary irradiation is the most effective form of therapy. Vaughan (18), reporting a series of 53 patients with acromegaly who were treated by pituitary irradiation, recommended 9 doses of 300 r each on successive days through 3 different portals. He observed as a result, prompt symptomatic relief of headache and visual impairment, cessation of polydipsia and polyuria, improvement of acromegalic myxedema and personality

changed. The tumor should be considered radio resistant but the treatment should nevertheless be repeated in 2 or 3 months. If, then, no remission is produced, the tumor should be considered as definitely radio resistant. He warned that the total dose of 2700 r may be followed by a period of lethargy, lowered vitality and by a lowered basal metabolic rate, that the patient may become uncomfortable and susceptible to infections and complications, but that usually he returns to normal after 1 or 2 months. Armed with this knowledge, the patient, as well as his physician, may be saved unnecessary discouragement over the immediate results of pituitary irradiation. We believe, however, that the ultimate success of radiotherapy in acromegaly is achieved by application of repeated series of adequate dosage. One should not be content merely to relieve the headache and improve the visual fields, but one should exert every effort to control the endocrinopathic hyperactivity. Subsequently one should not wait until headache and visual disturbances have recurred before repeating irradiation. One should be ready to apply therapy at the first signs of increasing endocrine activity. Thus, the emphasis must be placed squarely on alert and scrutinizing follow up. Since it is very easy to lose perspective in a disease of such long duration and such insidious course, one of us (M. B. G.) has devised a tabular chart for a periodic check up of acromegals (table 1).

**Sex hormones** Marrian and Butler (19) showed that large doses of estrogen decreased pituitary activity while small doses might stimulate it. Kirklin and Wilder (20) and Schrire and Sharpey Schafer (13) utilized this principle in the treatment of acromegaly. The latter workers used estradiol benzoate in women and testosterone propionate in men. We believe that these and related substances are valuable adjuvants to therapy when they are indicated. In our own experience two patients have been benefited by such treatment (21).

**Surgical therapy** We deplore the laissez faire policy which characterizes the treatment of acromegals in whom life or vision are not immediately threatened.

Should not the surgical approach to this problem be considered more often in cases of young and early acromegals to the end that such monstrosities as the patient in case 2 may be prevented? Surely, neurosurgery, with its ever receding percentage of fatalities, deserves a more prominent place in the treatment of acromegaly for endocrinopathic reasons alone, even when signs of increased intracranial pressure are absent. The sella turcica in this disease is greatly enlarged in the majority of cases and therefore is readily accessible to the expert neurosurgeon.

Strikingly illustrative of this argument is a recent experience of the authors, both of whom were called in consultation in the case of a 23 year old girl whose

TABLE 1. PROGRESS CHART FOR ACROMEGALICS

| Name                                 | No.  | Sex                 | S | M | W | D |
|--------------------------------------|------|---------------------|---|---|---|---|
| Date of Birth                        |      | Race                |   |   |   |   |
| Date of Onset                        | Age  | Earliest Symptoms   |   |   |   |   |
| Date First Seen                      | Age  | Presenting Symptoms |   |   |   |   |
| Skeletal changes                     | Date |                     |   |   |   |   |
|                                      |      |                     |   |   |   |   |
| Headache                             |      |                     |   |   |   |   |
| Visual disturbances (subj and obj)   |      |                     |   |   |   |   |
| Excessive sweating<br>Night sweats   |      |                     |   |   |   |   |
| Somnolence<br>Lethargy, weakness     |      |                     |   |   |   |   |
| Catamenia<br>Libido<br>Potentia      |      |                     |   |   |   |   |
| Polyuria<br>Polydipsia               |      |                     |   |   |   |   |
| Polyphagia                           |      |                     |   |   |   |   |
| Weight                               |      |                     |   |   |   |   |
| Pulse<br>Blood pressure              |      |                     |   |   |   |   |
| Urinalysis                           |      |                     |   |   |   |   |
| Blood sugar<br>Blood sugar tolerance |      |                     |   |   |   |   |
| Blood chemistry                      |      |                     |   |   |   |   |
| B M R                                |      |                     |   |   |   |   |
| Photographs                          |      |                     |   |   |   |   |
| Dental casts                         |      |                     |   |   |   |   |
| Therapy<br>Surgery<br>X Ray<br>Other |      |                     |   |   |   |   |
| Remarks                              |      |                     |   |   |   |   |

acromegaly was complicated by diabetes mellitus, renal impairment, malignant hypertension, tachycardia, goiter, increased basal metabolic rate, amenorrhea, heterosexual hypertrichosis and somewhat enlarged clitoris. Even before the age of 20 years this girl had had some limitation of the visual fields which seemingly was corrected by pituitary irradiation. Nevertheless, when she was 21 years old, one of us (H. L.) considered the acromegaly in this patient to be in a progressive hyperactive state and urged subtotal hypophysectomy because postponement of such radical therapy involved the greater hazard of a more

TABLE 2. ANTHROPOMETRIC MEASUREMENTS OF CASE 1

| Taken August 14, 1928 | Patient's age, 28 yr. |
|-----------------------|-----------------------|
| Weight                | 192 lb.               |
| Height, standing      | 167.7 cm.             |
| sitting               | 92.0 cm.              |
| Chest, circumference  | 103.8 cm.             |
| breadth (transverse)  | 32.4 cm.              |
| depth                 | 27.6 cm.              |
| Shoulder, biacromial  | 40.6 cm.              |
| Pelvis, bicristal     | 29.8 cm.              |
| Head, length          | 19.7 cm.              |
| breadth               | 15.9 cm.              |
| ear height            | 12.9 cm.              |
| face length           | 12.7 cm.              |
| face breadth          | 15.8 cm.              |
| nose length           | 5.2 cm.               |
| nose breadth          | 4.7 cm.               |
| Hand, length          | 18.8 cm.              |
| breadth               | 9.8 cm.               |

dangerous condition later. The patient and her family refused operation. A year later radiation therapy was again attempted but two courses proved ineffectual. Three months after the last treatment surgical intervention became imperative because of sudden and severe visual impairment. The patient died 12 hours postoperatively from respiratory failure due to uncontrollable edema of the brain. Therapy in this case had been too little and too late.

In conclusion, therefore, we urge consideration of a more radical attitude toward partial hypophysectomy at least in those patients who have not responded completely to adequate pituitary irradiation. This recommendation is based on the same thesis as that which justifies removal of a parathyroid adenoma for osteitis fibrosa cystica (hyperparathyroidism), of an islet cell tumor for hyperinsulinism, of a pheochromocytoma for paroxysmal hypertension, of adrenal cortical tumors which cause sexual precocity or masculinization, of granulosa cell tumors, of arrhenoblastoma and finally, subtotal removal of the

TABLE 3. ANTHROPOMETRIC MEASUREMENTS OF Case 2

|  | August 7, 1928 | July 25, 1936 (post-mortem) |
|--|----------------|-----------------------------|
| Weight   | 268 lb.        | 265 lb. ±                   |
| Height, standing                                   | 178.2 cm.      | 188 cm.                     |
| sitting  | 94.0 cm.       |                             |
| Head, occipital frontal circumference              |                | 62.9 cm.                    |
| occipito-supraorbital circumference                |                | 87.3 cm.                    |
| bregma mental                                      |                | 78.2 cm.                    |
| length   | 21.9 cm.       | 25.4 cm.                    |
| breadth  | 16.3 cm.       |                             |
| ear height   | 13.7 cm.       |                             |
| Face, length                                       | 16.5 cm.       |                             |
| breadth  | 16.1 cm.       |                             |
| Nose, length                                       | 6.8 cm.        |                             |
| breadth  | 5.0 cm.        |                             |
| Neck   |                | 43.2 cm.                    |
| Thorax, circumference at 4th costosternal junction | 120.0 cm.      | 112.0 cm.                   |
| 7th  |                | 117.5 cm.                   |
| 10th   |                | 116.2 cm.                   |
| breadth (transverse)                               | 36.8 cm.       |                             |
| depth (AP) (unsatisfactory)                        | 33.7 cm.       |                             |
| Torso, length—acromion to AS spine                 |                | 57.8 cm.                    |
| 7th cervicle to tip of coccyx                      |                | 66.0 cm.                    |
| circumference at level of trochanters              |                | 112.0 cm.                   |
| Shoulder, bi-acromion                              | 42.2 cm.       |                             |
| Arms, length, acromion to tip of 2nd finger        |                | 88.8 cm.                    |
| acromion to olecranon                              |                | 40.4 cm.                    |
| olecranon to styloid of ulna                       |                | 32.8 cm.                    |
| circumference of biceps of forearm                 |                | 30.5 cm.                    |
|  |                | 24.1 cm.                    |
| Hands, greatest length, dorsal                     | 21.4 cm.       | 21.5 cm.                    |
| palmar   |                | 18.4 cm.                    |
| circumference, heads of metacarpals                |                | 27.9 cm.                    |
| thumb at first phalanx                             |                | 9.5 cm.                     |
| 1st finger   |                | 9.5 cm.                     |
| 2nd finger   |                | 9.5 cm.                     |
| 3rd finger   |                | 9.2 cm.                     |
| 4th finger   |                | 9.0 cm.                     |
| at wrist   |                | 21.9 cm.                    |
| breadth  | 11.2 cm.       |                             |
| Pelvis, bi-trochanteric                            | 37.0 cm.       |                             |
| Legs, circumference, mid-thigh                     |                | 49.0 cm.                    |
| calf   |                | 34.7 cm.                    |
| malleolus  |                | 29.2 cm.                    |
| length—AS spine to tip of 1st toe                  |                | 108.0 cm.                   |
| trochanter to head of fibula                       |                | 38.8 cm.                    |
| Feet, length, heel to top of first toe             |                | 29.0 cm.                    |
| circumference, mid tarsal                          |                | 27.3 cm.                    |
| heads of metatarsals                               |                | 27.3 cm.                    |
| great toe  |                | 12.0 cm.                    |

thyroid for hyperthyroidism. Radical reduction or excision of the hyperfunctioning tissue constitutes the most logical and the most direct approach. The risks involved are not excessive as compared to the hideous deformities and dangerous complications which almost always eventuate in neglected acromegals. Of this disease it may truly be said, 'Time marches on'.

We are indebted to Dr. Robert Stone and Dr. J. Williams, roentgenologists and dosage of pituitary technique knowledge, the opportunity of autopsies performed by Dr. Jesse Carr, and Dr. C. E. Smith and Dr. Dale Barbour as well as the Department of Pathology, Stanford University Medical School (case 3). We appreciate the advice and cooperation of Dr. Howard Naffziger and his associates of the Department of Neurosurgery (case 2).

#### ADDENDA

The following statistical information is added for the benefit of those readers who may be especially interested.

#### Synopsis of Roentgen ray Therapy

**Case 1** In 1923 the patient received a course of pituitary irradiation the amount of which is impossible to determine but which apparently did not produce epilation. Between June 4 and July 8, 1929, he received 2 treatments to each temporal region on a 120 K V apparatus, directed at a field  $12 \times 12$  cm. Apparently 250 r were administered to each side of the head. In 1931 treatment was given on a 200 K V apparatus with a filter of 0.5 mm Cu and 1 mm Al at a 50 cm focus skin distance over an area 4 cm in diameter. Twelve treatments were given at weekly intervals, 6 to the right and 6 to the left temporal region, or a total of 1050 r to each side. Between Dec. 13, 1933, and June 7, 1934, he received 18 treatments with rotation through 3 portals, the right temporal, the left temporal and the anterior. A 200 K V apparatus was used with a filter of 0.2 mm Sn, 0.25 mm Cu and 1 mm Al at a 50 cm skin target distance. The area irradiated was  $6 \times 6$  cm. In all 1200 r were given through each portal, or a total of 3600 r.

**Case 2** The patient was treated to the right side of his head, aiming at the pituitary, on July 20 and on Aug. 21, and to the left side of his head, aiming at the pituitary, on July 31 and on Aug. 28, 1923. It is impossible to estimate the number of roentgens administered during the treatments given in 1923. A 10 inch spark gap apparatus was said to have been used. The filter was 0.5 mm Cu and 1 mm Al. The distance of the target was 14 in. On July 20, 280 milliamperes minutes were given, on July 31, about 400, on Aug. 21, 300, and on Aug. 28, 420. The closest estimate of the dosage would be 15 r to every 10 milliamperes minutes.

**Case 3** The patient received 4 treatments of 200 r each to the right and left temporal regions on June 20, 24, 28 and Aug. 20, 1935. A 200 K V apparatus was used with a filter of 0.5 mm Cu and 1 mm Al. The focus skin dis-

tance was 40 cm and the area irradiated was 9 cm in diameter. The total dose was 800 r (in air) to each temporal area.

**Case 4** The patient first received roentgen ray treatment in 1928. On Nov. 2 and 7, she was treated to the left side of the head aiming at the pituitary and on Nov. 5 and 9, to the right side of the head aiming at the pituitary. On each occasion she received 150 milliamperes minutes with an apparatus running at 120 K V. The radiation was filtered through 0.25 mm Cu and 1 mm Al. The distance of the skin target was 15 in. Calculating from our present knowledge, we would say that between Nov. 2 and 9, 1928, the patient received about 350 r at each treatment, or a total of 700 r to the left and 700 r to the right side.

The patient was again treated in November, 1929, at which time the same fractions were given. Similar treatments were administered between Nov. 1 and 11, with the exception that 3 treatments were given to the left (Nov. 1, 6 and 11) and 2 to the right side (Nov. 4 and 6).

In 1938 most of the treatment was given on the 1000 K V apparatus with filtration of 2 mm of lead. The treatments were rotated through from the right lateral, the left lateral and the anterior portals, so that between April 21 and May 4 the patient received treatment almost every day, the amount being 850 r (in air) to the left side and to the anterior field and 900 r to the right lateral field.

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# Carbohydrate Metabolism of Animals Treated with Methyl Testosterone and Testosterone Propionate<sup>1</sup>

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## [Androgens and Carbohydrate Metabolism]

THAT THE USE of methyl testosterone in patients is followed by a decrease in tolerance for glucose has been reported (1). In an attempt to explain the mechanism involved, studies have been extended to rabbits. Glucose tolerance and liver and muscle glycogen have been determined when no treatment has been given, and when methyl testosterone and testosterone propionate have been administered. The fact that there is a marked increase in the basal metabolic rate of the animal treated with methyl testosterone suggested that the hypermetabolism itself might be affecting the glucose tolerance in a manner similar to that operative in hyperthyroidism. To study this, determinations were made of the glucose tolerance of thyroidectomized rabbits before and after treatment with methyl testosterone. Rats were also treated with methyl testosterone and the values for liver glycogen compared with those in normal controls. Similarly, the liver glycogen of hypophysectomized rats without treatment and with methyl testosterone therapy were compared.

### EXPERIMENTAL METHODS

*Rabbits; normal animals.* Adult male rabbits ranging in weight from 2.7 to 3.5 kg. were used. They were fed a constant diet of oats, hay, and carrots. Water was allowed ad libitum. The food was withheld for 24 hours before the beginning of a test period. Glucose tolerance was determined. Seven and one-half gm. of glucose dissolved in 35 cc. of water was given by stomach tube for the oral tests. Fifteen cc. of a 50 per cent glucose solution was injected for the intravenous tests. Blood samples were collected from the ear vein 0, 0.5, 1, 2, 3, and 4 hours after the administration of glucose. Blood glucose was determined using the Somogyi modification of the micro-Shaffer-

Hartmann method (2). The urine excreted during the test period was collected and tested for glucose. If any was present, a quantitative determination using the quantitative Benedict's reagent was made (2b).

Methyl testosterone was administered orally, daily in doses of 5, 10, or 20 mg. The rabbits receiving the testosterone propionate were injected daily with 5, 7.5, or 10 mg. of the hormone dissolved in sesame oil. The sugar tolerance curves were determined from time to time during the period of treatment. When no further modification in the curve occurred, the animals were killed, and the liver and muscle glycogen content were determined (3). The rabbits were placed under nembutal anesthesia, the gastrocnemius muscle was dissected out as rapidly as possible and immediately frozen in dry ice. The liver was quickly exposed and representative sections from each lobe were dropped into 30 per cent KOH solution. The testes, seminal vesicles, prostate, adrenals, pituitary, and a piece of pancreas, liver, and kidney were saved for histological study. Normal untreated rabbits which had been on the standard diet for at least 4 weeks were used for normal control glycogen determinations.

*Thyroidectomized animals.* Rabbits were thyroidectomized under nembutal anesthesia. Following operation they were injected with 10 units of parathormone and were given 5 grains of calcium lactate and 50 units of vitamin D daily. After two weeks the parathormone was discontinued, but the other treatment was given throughout the experimental period.

*Rats.* A group of 22 normal male rats 104 days of age and of approximately the same body weight was selected. They were fed a constant diet of Purina dog chow, bread, and lettuce. Eleven of the animals were given 5 mg. of methyl testosterone per day orally and 11 were used as controls. After 38 days of treatment they were killed 24 hours after withdrawal of food, and the liver glycogen levels were determined. Two groups of male rats were hypophysectomized.

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TABLE 1 SUGAR TOLERANCE OF RABBIT 6 TREATED WITH METHYL TESTOSTERONE

| Date    | Days of Treatment with 10 mg Methyl Testosterone | Body Weight, kg | Dextrose, Given, 7.5 gm | Urine Glucose gm | Blood Sugar mg/100 cc |      |      |      |      |      |
|---------|--|-----------------|-------------------------|------------------|-----------------------|------|------|------|------|------|
|         |  |                 |                         |                  | Fasting               | ½ hr | 1 hr | 2 hr | 3 hr | 4 hr |
| 7/10/41 | 0  | 2.88            | Orally                  | 0                | 92                    | 149  | 174  | 166  | 124  | 107  |
| 7/14/41 | 0  | 2.85            | Orally                  | 0                | 100                   | 141  | 174  | 162  | 115  | 115  |
| 7/31/41 | 8  |                 | Orally                  | 0                | 100                   | 141  | 166  | 149  | 107  | 107  |
| 8/7/41  | 15   | 2.84            | Orally                  | 0                | 107                   | 182  | 190  | 153  | 107  | 100  |
| 8/14/41 | 22   |                 | Orally                  | 0                | 100                   | 198  | 224  | 174  | 152  | 100  |
| 8/21/41 | 29   | 2.81            | Orally                  | 0                | 107                   | 190  | 215  | 174  | 141  | 100  |
| 9/3/41  | 42   | 2.82            | Orally                  | 0                | 100                   | 190  | 207  | 174  | 149  | 107  |
| 7/17/41 | 0  | 2.88            | Intravenously           | 1.8              | 100                   | 524  | 321  | 124  | 100  | 83   |
| 7/21/41 | 0  |                 | Intravenously           | 1.8              | 97                    | 518  | 330  | 127  | 88   | 97   |
| 8/27/41 | 35   | 2.83            | Intravenously           | 2.16             | 100                   | 487  | 380  | 157  | 115  | 107  |

The first group was 152 days of age at operation, and the second group was 88 days old. Half of each group was given 5 mg of methyl testosterone per day, starting the second day after operation, half received no treatment and were used as controls. Thirty days after operation they were killed 10 hours after withdrawal of food, and liver glycogen values were determined. Each animal was checked for completeness of hypophysectomy, the testes were weighed.

## RESULTS

**Rabbits.** Following 22 days of treatment with 10 mg of methyl testosterone daily, the sugar tolerance curve in the rabbit showed a definite deviation from normal. The level to which the blood sugar rose was increased, and the return to normal was prolonged. A modification in the curves following both the oral and intravenous administration was observed. After 15 days a questionable deviation from normal was observed. After 29 days the maximum variation was established, and further treatment for as long as 45 days produced no additional effect. Table 1 gives the data on rabbit 6 and are typical of that observed in

the other 8 rabbits similarly treated. The dosage of methyl testosterone appeared to play little part in the time of onset of the change in sugar tolerance. Rabbits receiving 10 mg per day showed a modified tolerance at about the same time as those receiving 20 mg per day. Two of the 3 animals receiving 5 mg per day showed a modified curve in 29 days, whereas the third showed no significant change until after 36 days of treatment.

In 6 animals, after extensive treatment with methyl testosterone and after a maximum change had been observed in the sugar tolerance, additional carbohydrate (15 gm sugar per day) was included in the diet. One week later the sugar tolerance curves were found to be within normal limits. In these animals, as in other animals with depleted glycogen stores, there appeared to be a diminution in glucose tolerance. Provided with additional carbohydrate, the animal was able to restore the glycogen stores to normal levels. Figure 2 shows the glycogen values in the 3 animals killed at this time. Two weeks after the withdrawal of the extra carbohydrate, the 3 rabbits again showed a decreased tolerance (table 2).

TABLE 2 BLOOD GLUCOSE VALUES IN RABBIT 15 RECEIVING METHYL TESTOSTERONE AND HIGH CARBOHYDRATE DIET

| Date     | Treatment  | Glucose, mg per 100 cc of Blood |      |      |      |      |      |
|----------|--|---------------------------------|------|------|------|------|------|
|          |  | Fasting (after 7.5 gm glucose)  | ½ hr | 1 hr | 2 hr | 3 hr | 4 hr |
| 10/3/41  | None   | 83                              | 174  | 194  | 149  | 122  | 100  |
| 10/24/41 | None   | 92                              | 182  | 182  | 149  | 107  | 83   |
| 12/23/41 | Methyl test, 5 mg per day, 39 days   | 92                              | 188  | 215  | 169  | 141  | 115  |
| 1/29/42  | Methyl test 5 mg per day 69 days. Last 14 days given 15 gm additional carbohydrate in diet | 92                              | 190  | 190  | 149  | 107  | 96   |
| 1/30/42  | Added carbohydrates withdrawn from diet  |                                 |      |      |      |      |      |
| 2/19/42  | Methyl test, 5 mg per day, 90 days   | 83                              | 188  | 207  | 166  | 141  | 107  |

Treatment with testosterone propionate, on the other hand, did not significantly modify the sugar tolerance curves of the treated rabbits. Treatment for as long as 55 days with 10 mg. of testosterone propionate per day was ineffective in modifying the

testosterone to maintain a normal liver glycogen. The muscle glycogen level of neither the animals treated with testosterone propionate, or methyl testosterone, nor those receiving the methyl testosterone and high carbohydrate diet was significantly

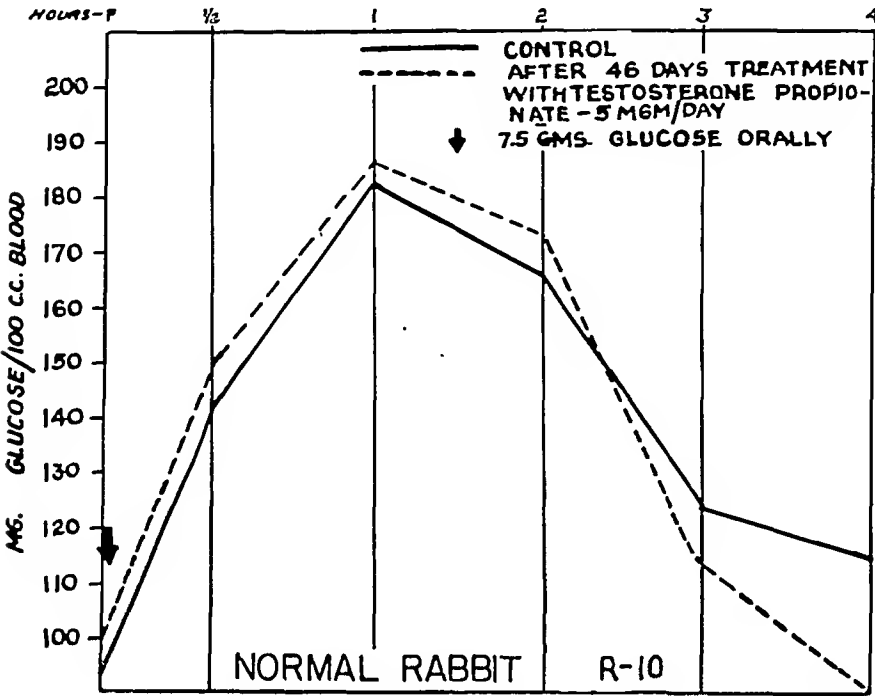


Fig. 1. BLOOD SUGAR CURVES of a normal rabbit before and after treatment with testosterone propionate.

tolerance for glucose. Figure 1 shows the results obtained on R10 and is typical of the values obtained on the 5 rabbits thus treated.

The rabbits receiving methyl testosterone and testosterone propionate showed no increase in body weight. A gain in weight, caused chiefly by retention of fluid, frequently is observed in the human being receiving large amounts of these hormones.

Figure 2 shows the liver and muscle glycogen values of the normal rabbits and of the animals receiving treatment with methyl testosterone and testosterone propionate. The average control level of liver glycogen was 0.568 gm. per cent, the range being from 0.445 to 0.740 gm. per cent. In the animals treated with methyl testosterone the average liver glycogen was 0.338 gm. per cent, the range being from 0.242 to 0.417 gm. per cent. In the animals treated with testosterone propionate the average liver glycogen was 0.757 gm. per cent, the range being from 0.611 to 0.840 gm. per cent. In the animals receiving methyl testosterone and a high carbohydrate diet, the average liver glycogen was 0.650 gm. per cent, the range being from 0.532 to 0.800 gm. per cent. The level of liver glycogen thus was markedly decreased following prolonged treatment with methyl testosterone and was somewhat increased following testosterone propionate treatment. A high carbohydrate diet enabled the animal treated with methyl

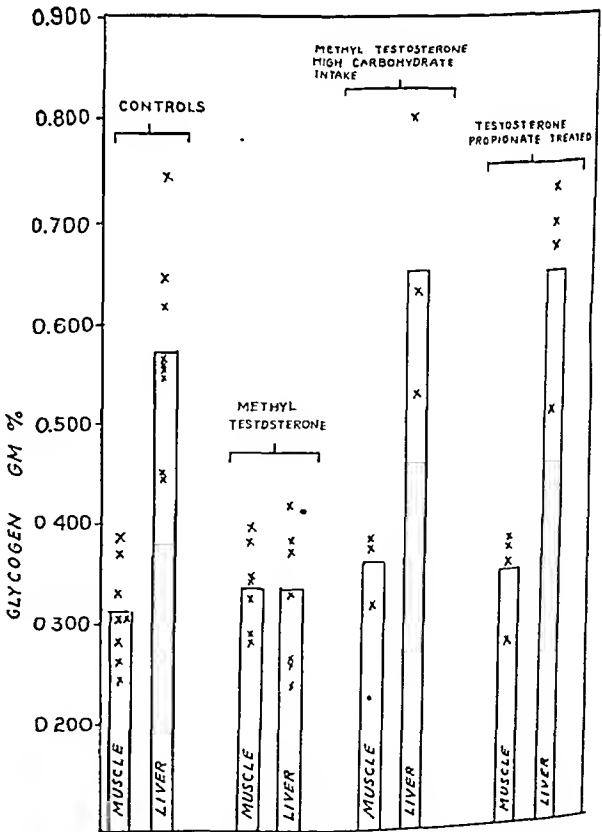


Fig. 2. MUSCLE AND LIVER GLYCOGEN of rabbits treated and untreated with methyl testosterone.

altered from the normal. The average control level of muscle glycogen was 0.311 gm. per cent (range 0.248 to 0.385 gm. per cent). The average for the animals treated with methyl testosterone was 0.338 (range 0.283 to 0.387) gm. per cent; that for the animals receiving methyl testosterone and a high carbohydrate diet was 0.36 (range 0.322 to 0.380) gm. per cent; and that for the group treated with testosterone propionate was 0.351 (range 0.284 to 0.384) gm. per cent.

**Thyroidectomized animals.** The studies of glucose tolerance of the thyroidectomized rabbits were started 5 weeks after operation. After oral and intravenous tolerance curves had been determined, treatment with methyl testosterone was instituted. Figure 3 summarizes the results obtained on R18, one of the 3 animals thus treated. Any modification in the glu-

TABLE 3. EFFECT OF METHYL TESTOSTERONE ON LIVER GLYCOGEN OF NORMAL AND HYPOPHYSECTOMIZED RATS

| Rat No. | Age at Operation or Beginning of Experiment, days | Treatment                  | Liver Glycogen, gm. % | Testes Weight, gm. |
|---------|---|----------------------------|-----------------------|--------------------|
| 1       | 104   | None                       | .232                  | 2.9                |
| 2       | 104   | None                       | .380                  | 2.9                |
| 3       | 104   | None                       | .232                  | 2.8                |
| 4       | 104   | None                       | .346                  | 2.2                |
| 5       | 104   | None                       | .339                  | 2.4                |
| 6       | 104   | None                       | .378                  | 2.8                |
| 7       | 104   | None                       | .298                  | 2.3                |
| 8       | 104   | None                       | .320                  | 2.6                |
| 9       | 104   | None                       | .216                  | 2.0                |
| 10      | 104   | None                       | .274                  | 2.5                |
| 11      | 104   | None                       | .342                  | 2.8                |
| Average |   |                            | .306                  | 2.57               |
| 1-T     | 104   | 5 mg. meth. testost. / day | .247                  | 1.4                |
| 2-T     | 104   | 38 days                    | .221                  | 1.5                |
| 3-T     | 104   | 38 days                    | .211                  | 1.5                |
| 4-T     | 104   | 38 days                    | .194                  | 1.6                |
| 5-T     | 104   | 38 days                    | .245                  | 1.5                |
| 6-T     | 104   | 38 days                    | .190                  | 1.0                |
| 7-T     | 104   | 38 days                    | .218                  | 1.9                |
| 8-T     | 104   | 38 days                    | .144                  | 1.9                |
| 9-T     | 104   | 38 days                    | .220                  | 1.5                |
| 10-T    | 104   | 38 days                    | .236                  | 1.7                |
| 11-T    | 104   | 38 days                    | .123                  | 1.7                |
| Average |   |                            | .209                  | 1.56               |
| 2-0     | 88  | hypophysectomized          | 1.38                  | 1.1                |
| 6-0     | 88  | hypophysectomized          | 1.46                  | 0.5                |
| 4-0     | 88  | hypophysectomized          | 1.62                  | 0.9                |
| 5-0     | 88  | hypophysectomized          | 1.48                  | 1.0                |
| 7-0     | 88  | hypophysectomized          | 1.33                  | 0.9                |
| 3-0     | 88  | hypophysectomized          | 2.36                  | 2.2                |
| 9-0     | 152   | hypophysectomized          | 1.38                  | 0.5                |
| 10-0    | 152   | hypophysectomized          | .88                   | 0.4                |
| 11-0    | 152   | hypophysectomized          | 1.40                  | 0.7                |
| 14-0    | 152   | hypophysectomized          | 1.63                  | 0.8                |
| 15-0    | 152   | hypophysectomized          | 1.55                  | 0.6                |
| 8-0     | 152   | hypophysectomized          | 1.18                  | 0.7                |
| 13-0    | 152   | hypophysectomized          | 0.80                  | 1.0                |
| 12-0    | 152   | hypophysectomized          | 1.78                  | 2.6                |
| 16-0    | 152   | hypophysectomized          | 2.46                  | 2.9                |

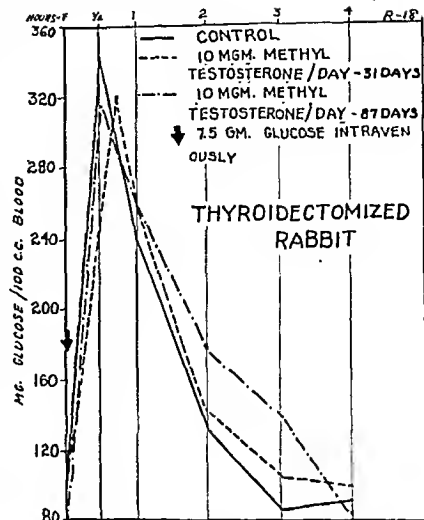


Fig. 3. BLOOD SUGAR CURVES of a thyroidectomized rabbit before and after treatment with methyl testosterone.

ose tolerance of the thyroidectomized animal following methyl testosterone treatment was very slight, and the period of treatment before the questionable change was much longer than that required for maximum change in the normal animal treated with methyl testosterone.

**Rats.** Table 3 summarizes the results on the unoperated rats and the hypophysectomized animals. In the unoperated group a decrease in liver glycogen was observed following hormone administration which was similar to that observed in the rabbits treated with methyl testosterone. In the operated groups the range of liver glycogen levels was so great that definite conclusions could not be drawn. However, there appeared to be no significant variation between the untreated operated animals and the group treated with methyl testosterone.

#### DISCUSSION

The fact that no significant change in the muscle glycogen of the rabbits was observed following treatment with testosterone propionate is in agreement with the findings of Gaunt et al. (4) in rats. However, they observed no significant modification in the liver glycogen. That our animals received treatment for a very much longer period may account for the difference. Although the slight increase found by us appears to be statistically significant, the change is small in comparison with that produced by cortical extract and some other hormone preparations.

Cahone et al. (5) reported a decreased muscle glycogen in guinea pigs following testosterone propionate treatment. The range of glycogen levels in their group of control animals (0.938 to 5.372 per cent) and of treated animals (0.764 to 4.509 gm. per cent) was so great that the decrease, as judged by the means of 3.11 and 2.04, probably is not significant.

Winter et al. (6) reported that phlorhizin glycosuria in the rat is greatly inhibited by pretreatment with testosterone. They attributed the decrease in glycosuria to the protective action of the testosterone on the convoluted tubules of the kidney. It would appear possible that part of the decreased glycosuria might be due to decreased glycogen stores similar to those observed by us following methyl testosterone treatment.

The modification in glucose tolerance and carbohydrate storage observed following the prolonged administration of methyl testosterone seems to depend upon the action of other endocrine glands. In the absence of the thyroid or pituitary gland the changes were not observed. There is no proof that the whole modification is dependent upon these glands, and other mechanisms may also be involved. The fact that the animal treated with methyl testosterone was able to maintain normal carbohydrate stores and showed a normal glucose tolerance if greatly increased amounts of carbohydrate were given in the diet would indicate that the disturbance was due to increased utilization rather than to an inability to store carbohydrate.

#### SUMMARY

The glucose tolerance of rabbits was decreased following prolonged treatment with large doses of methyl testosterone. No modification in glucose tolerance was observed following a similar period of treatment with testosterone propionate. Thyroidectomized animals showed no apparent modification or a very slight decrease in sugar tolerance following prolonged treatment with methyl testosterone.

The level of liver glycogen of rabbits treated with methyl testosterone, and showing a modified sugar tolerance, was well below that of untreated normal controls. Following testosterone propionate treatment the liver glycogen was slightly but significantly increased. The muscle glycogen of neither group of treated animals was altered significantly.

The liver glycogen of rats treated with methyl testosterone was lower than that of untreated controls. There appeared to be no significant difference between the liver glycogen level of hypophysectomized untreated rats and hypophysectomized rats receiving methyl testosterone.

In the absence of the thyroid or pituitary gland, no modification in glucose tolerance or carbohydrate storage was observed following prolonged administration of methyl testosterone.

We wish to thank Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J., for the methyl testosterone and testosterone propionate used in these experiments.

We are indebted to Dr. Owen Reeves for hypophysectomizing the rats.

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# Carbohydrate Metabolism of Patients Treated with Methyl Testosterone

## [Hypogonadism]

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THAT TREATMENT of patients with large doses of methyl testosterone for long periods of time results in a modification of sugar tolerance has been reported (1). Studies have been extended to determine the factors involved in producing this change. In rabbits treated with methyl testosterone a decreased sugar tolerance also has been observed. The liver glycogen of these animals was less than that of untreated controls (2). In an attempt to determine whether a modification in liver glycogen reserves occurs in the human being receiving methyl testosterone, estimations using the phlorhizin technic of Mirsky (3) have been made. The test is based on the assumption that, following phlorhizin, 'when the blood sugar level remains constant, all of the urinary sugar must have come from the liver. On the other hand, if there has been a fall in the blood sugar level, then the amount of sugar excreted in the urine is equal to the sum of that secreted by the liver plus the sugar equivalent to the decrease in the blood and tissues' (3). The basal metabolic rate and the glucose tolerance of the patients treated with methyl testosterone also were determined. Generally, the basal metabolic rate was markedly above the pretreatment level when the decrease in sugar tolerance was observed, and the amount of glucose of liver origin excreted following phlorhizin usually was decreased.

### METHODS AND MATERIALS

Eight cases of male hypogonadism were studied before any treatment was given (or during a period of withdrawal of therapy), and during treatment with large doses of methyl testosterone. Sugar tolerance curves were determined following the oral administration of 100 gm of dextrose. In the sugar tolerance tests the blood sugar values were determined by the method of Myers and Bailey (4). Basal metabolic rates were measured using the Sanborn Graphic

machine and the Mayo Clinic tables. Each test represented two runs. The hepatic glycogen reserves were measured by the phlorhizin method of Mirsky (3). Blood sugars were determined on venous blood by the Somogyi modification of the micro Shaffer Hartmann method (5). Blood acetone was determined by the method of van Slyke and Fitz (6, 7). Urinary nitrogen was determined by the Kjeldahl method (8). In some cases, when the patient was receiving methyl testosterone therapy, a diet high in carbohydrates was given to determine its effect upon the sugar tolerance and glycogen reserves during hormone treatment. The high carbohydrate diet consisted of 500 gm of carbohydrate with a total caloric value of 3000 calories.

### RESULTS

In some cases the administration of large doses of methyl testosterone was followed by a marked decrease in sugar tolerance. The decreased tolerance was usually associated with an increased basal metabolic rate. Table 1 summarizes the results on 7 of the patients.

Phlorhizin tests were made on 5 patients, the data on 4 of whom are included in table 1. Figure 1 summarizes the results on patient 4. Following treatment with methyl testosterone, the liver glycogen stores were 380 mg per kg of body weight. Upon withdrawal of therapy, they were 417 mg per kg of body weight or greater. As there was no drop in the blood glucose level, the amount of glycogen remaining in the liver at the end of the test was not indicated. With methyl testosterone therapy and an increased amount of carbohydrate in the diet, the liver glycogen stores were 464 mg per kg. At the end of the 6 hour phlorhizin test, when the glycogen stores were lowest the blood acetone showed an increase of 100 per cent. Acetone was present in the 5th and 6th hour urine specimens. The blood acetone was not significantly altered when no therapy was being taken or when a high carbohydrate diet was being ingested.

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The glycogen storage values were based on the following points. The blood-sugar level did not drop during the 6-hour phlorhizin test period when the patient had been receiving no therapy, or when the patient was on the high carbohydrate diet—methyl testosterone regimen. The blood sugar values fell 13 mg. during the 6-hour test period when the patient was receiving methyl testosterone therapy. Employing the 30 per cent figure for the mixing volume for 80 mg. daily the second month), he showed a markedly decreased sugar tolerance. At that time, following phlorhizin injection, he excreted 537 mg. glucose per kg. of body weight, of which 490 mg. was of liver origin. The blood acetone was increased by 53 per cent at the end of the 6-hour phlorhizin test. Five months later on the same therapy, the sugar tolerance was more normal (fig. 3). At that time, following phlorhizin 521 mg. of glucose per kg. of body weight,

TABLE 1. EFFECT OF METHYL TESTOSTERONE ON BLOOD GLUCOSE LEVELS IN HYPOGONADAL MEN

| Case | Diagnosis    | Treatment             |  | B. M. R.<br>% | Sugar Tolerance, Glucose, mg./100 cc.<br>at Hours |               |     |     |     |     |
|------|--------------|-----------------------|--|---------------|---|---------------|-----|-----|-----|-----|
|      |              | Duration,<br>days     | Methyl<br>testosterone<br>per day, mg. |               | 0   | $\frac{1}{2}$ | 1   | 2   | 3   | 4   |
| 1    | Hypogonadism | 30                    | 0                                      | -13           |   |               |     |     |     |     |
|      |              | 30                    | 0                                      | +3            | 97  | 122           | 130 | 98  | 104 |     |
|      |              | 19                    | 300 mg.                                | +2            | 118   | 224           | 213 | 241 | 161 | 120 |
| 2    | Hypogonadism | 35                    | 0                                      | -11           |   |               |     |     |     |     |
|      |              | 42                    | 0                                      |               | 104   | 207           | 127 | 94  | 76  |     |
|      |              | 19                    | 300 mg.                                | -3            | 109   | 213           | 187 | 200 | 125 |     |
| 3    | Hypogonadism | 60                    | 0                                      | -17           | 102   | 102           | 90  | 80  | 78  |     |
|      |              | 60                    | 100 mg.                                | +3            | 98  | 122           | 122 | 94  | 102 | 84  |
| 4    | Hypogonadism | 15                    | 0                                      | -1            |   |               |     |     |     |     |
|      |              | 18                    | 100 mg.                                |               | 96  | 160           | 210 | 168 | 68  | 58  |
|      |              | 120                   | 60 mg.                                 | +24           | 110   | 169           | 242 | 212 | 100 | 108 |
| 5    | Hypogonadism | 39                    | 0                                      | +1            | 102   | 116           | 90  | 108 | 78  |     |
|      |              | 49                    | 250 mg.                                | +27           | 130   | 190           | 168 | 173 | 130 | 79  |
| 6    | Hypogonadism | No previous treatment |  | -13           | 106   | 136           | 174 | 106 | 80  | 70  |
|      |              | 21                    | 100 mg.                                |               |   |               |     |     |     |     |
|      |              | 42                    | 200 mg.                                |               |   |               |     |     |     |     |
| 7    | Hypogonadism | 30                    | 300 mg.                                | ± 0           | 106   | 155           | 132 | 147 | 93  | 85  |
|      |              | 30                    | 100 mg.                                |               |   |               |     |     |     |     |
|      |              | 21                    | 200 mg.                                |               |   |               |     |     |     |     |
|      |              | 21                    | 300 mg.                                | -3            | 106   | 171           | 238 | 204 | 117 | 77  |
|      |              | 27                    | 0                                      | -3            | 138   | 202           | 187 | 143 | 82  | 82  |

sugar distribution in the body, as used by Mirsky, 3.78 gm. of the sugar excreted was from non-liver source. The increase in blood acetone was also of significance.

Patient 3 excreted 488 mg. of glucose per kg. of body weight, all of liver origin, when no therapy had been taken for 3.5 months. The blood acetone was unaltered at the end of the test period. When he had received 100 mg. of methyl testosterone per day for two months, 470 mg. glucose per kg. of body weight was excreted, of which 413 mg. was of liver origin (fig. 2). At the end of the 6-hour phlorhizin test the blood acetone had increased from 1.6 to 3.5 mg. per 100 cc. of blood.

When patient 5 had been receiving methyl testosterone for 2 months (70 mg. daily the first month, all of which was of liver origin, was excreted following phlorhizin injection. The blood acetone was not significantly modified at the end of the 6-hour test period.

In the case of patient 8, who had been receiving 50 mg. of testosterone propionate 3 times a week for 4 months, 353 mg. of glucose per kg. of body weight, all of which was of liver origin, was excreted following phlorhizin injection. The blood acetone was not increased at the end of the 6-hour test period. After he had been receiving methyl testosterone (100 mg. per day for 5 months), the glucose excretion following phlorhizin was 422 mg. per kg. of body weight, the source of which was the liver. At that time he showed a slightly modified glucose tolerance curve. The blood acetone was not significantly altered.

When therapy was withdrawn for two months, 316 mg of glucose per kg of body weight was excreted. All was of liver origin. There was no significant modification in blood acetone at the end of the 6 hour test.

Patient 6 excreted 381 mg of glucose per kg of body weight following phlorhizin when he had received no treatment. All of this was of liver origin. After 3 months of treatment with methyl testosterone (100 mg daily for 21 days, 200 mg daily for 42 days, and 300 mg daily for the 30 days immediately preceding the phlorhizin test) 365 mg of glucose per kg was excreted following phlorhizin, of which 318 mg was of liver origin. In the first test no acetone was present in any urine specimen. In the phlorhizin test following methyl testosterone treatment the urine showed acetone in the specimens collected for the 4th, 5th, and 6th hours after the initial injection.

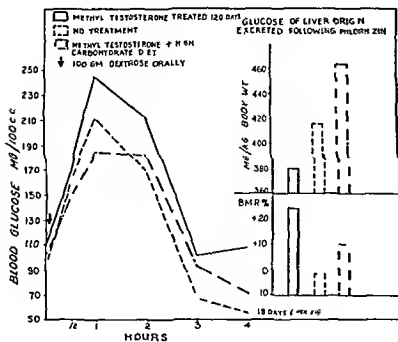


Fig 1

Patient 7 excreted 221 mg of glucose per kg of body weight, which was of liver origin, after he had been receiving large doses of methyl testosterone for 10 weeks. The blood acetone was increased from 1.5 to 5.5 mg per 100 cc at the end of the 6 hour phlorhizin test. The hippuric acid liver-function test at this time showed 3.0 gm of benzoic acid synthesized (equivalent to 100 per cent of normal). After therapy had been withdrawn for 27 days, 245 mg of glucose per kg of body weight, which was of liver origin, was excreted. The blood acetone was 1.7 mg per 100 cc of blood at the beginning of the 6 hour phlorhizin test and 2.1 mg at the conclusion of the test period.

Urine nitrogen was determined on aliquots of the pooled urine collected during the first 3 hours of the phlorhizin test period and the second 3 hours of the test. In no case was the nitrogen excretion significantly different in the two periods. This indicated that gluconeogenesis was not increased.

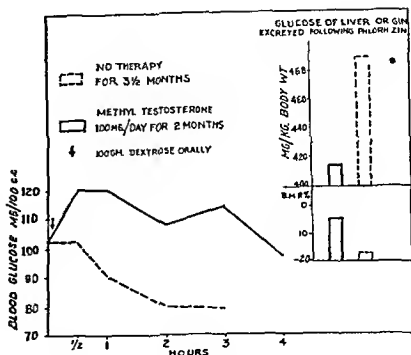


Fig 2

## DISCUSSION

The estimation of liver glycogen reserves, using the glucose excretion following phlorhizin as the basis of calculation, is open to certain fundamental criticism. Although the values thus estimated may not be the true ones, it is believed that repeated tests on the same individual are capable of showing actual changes in glycogen stores. It is also believed that greater significance can be placed on the decreased glycogen stores in patients following the use of methyl testosterone, since this change has been observed in treated animals in which the livers have been removed and glycogen values actually determined (2).

Winter et al. (6) reported that phlorhizin glycosuria in the rat is greatly inhibited by pretreatment with testosterone. They attributed this decrease to a modification in the epithelial cells lining the convoluted tubules of the kidney. No liver glycogen determinations were made on the testosterone treated rats.

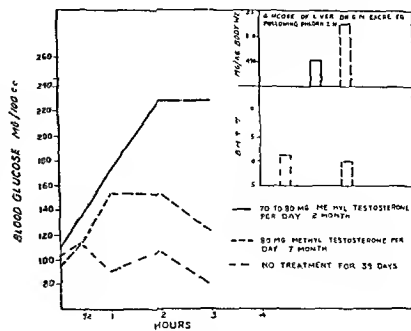


Fig 3



That the action of methyl testosterone on the kidney was responsible for the decreased excretion of glucose per kg. of body weight, of liver origin, seems unlikely, for in some cases the actual total excretion of glucose was as great in the treated as in the untreated patient. A significant percentage of it, however, originated from the blood and body fluids, as a marked decrease in blood glucose was observed at the end of the 6-hour test period.

In the case of *patient 5* it is difficult to explain the greater sugar tolerance after 7 months of treatment with methyl testosterone than after 2 months. Some compensatory mechanism may have become effective in the interval. The importance of the nature of the diet in modifying sugar tolerance cannot be disregarded. While the patients were not on a controlled diet, they were questioned as to any change in eating habits or food intake. This patient was unaware of any such change.

The unusually low glycogen reserves in *patient 7* are difficult to interpret. He was accustomed to eating unusually large amounts, and his diet represented a very large total carbohydrate intake. The food intake was essentially constant throughout the period of observation.

The results on *patient 8* cannot be evaluated to indicate change in glycogen stores, for at no time were the reserves exhausted following phlorhizin, as indicated by the maintained blood-sugar level and the absence of increased blood acetone.

The decreased glycogen reserves during methyl testosterone treatment could not be attributed to liver damage, for there was no evidence of decreased liver function, as judged clinically or by hippuric acid and bromsulfalein liver function tests.

#### SUMMARY

Following continued treatment with methyl testosterone, some patients showed a decreased sugar tolerance. In the majority of cases this decrease was accompanied by an increased basal metabolic rate. In one patient an increase in carbohydrate in the diet resulted in the return to normal of the modified sugar tolerance and increased glycogen stores. Liver glycogen reserves were estimated by the phlorhizin method of Mirsky. There was less stored glycogen in the liver following methyl testosterone treatment. This was in agreement with the finding that the liver glycogen of rabbits was decreased following methyl testosterone therapy.

We wish to thank Dr. Max Gilbert of the Schering Corp., Bloomfield, N.J., for the methyl testosterone used in these studies.

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# Insulin Resistance in Diabetes Mellitus

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SINCE THE BEGINNING of the insulin era, the sub-  
ject of insulin resistance has become one of in-  
creasing interest. Root (1), in 1929, termed those  
cases insulin resistant which required more than 100  
units daily to maintain proper carbohydrate balance.  
He pointed out that temporary resistance to insulin,  
so commonly encountered for a brief period in the  
comatose diabetic, properly should not be included  
under such a designation. He estimated, on the basis  
of animal experiments, that a completely pancre-  
atized man would require 200 to 300 u daily. Undis-  
puted cases of complete insulin resistance in man  
would thus be those which have a daily insulin re-  
quirement above this.

There have been published a number of isolated  
reports of patients who have required an abnormally  
large amount of insulin. These have been summarized  
during the past year in a paper by Martin, Martin,  
Lyser and Strouse (2). To these may be added two  
cases of Marble, Fernald and Smith (3), one requiring  
300 to 1750 u daily for 2 months, the other 350 to  
2000 u daily for over 7 months, and the patient re-  
ported by Levi and Friedman (4) who received an  
average of 1621 u daily for 47 days, the maximum  
daily dosage being 4000 u.

No real advance in the understanding of this re-  
sistance to insulin was made until recently, when the  
studies of Houssay (5) and of Long (6) began to throw  
an entirely new light on carbohydrate metabolism.  
Young (7) has investigated the problem from the  
laboratory standpoint, and Glen and Eaton (8) and  
Wiener (9) from the clinical point of view.

We are reporting a case of insulin resistance in a  
patient with diabetes mellitus who for almost 4  
months received an average daily dose of 1195 u, a  
maximum daily dose of 2460 u, with a total dosage of  
129,470 u. Certain investigative studies have been  
performed in an endeavor to throw light on the  
mechanism of insulin resistance.

## CASE REPORT

C.A.K., S.F.H. No. 257261, was a 64 year-old married  
male leather worker of Irish Portuguese parentage who  
was first seen at the Stanford Hospital Outpatient De-  
partment on Jan. 28, 1939. The diagnosis of pulmonary  
tuberculosis was made. Sugar was found in the urine at  
this time but the patient did not return to the clinic. On  
Oct. 5, 1939, he was seen again and had then lost 17 lb  
(7.7 kg) in weight. The additional diagnosis of diabetes  
mellitus was made at this time. He attended the clinic a  
few times and on Oct. 28, 1939 was admitted to the  
*Tuberculosis Division of the San Francisco Hospital*.

**Family history.** Father and mother died at 66 and 57  
years of unknown causes. One brother died at 17 of  
tuberculosis, and another brother died at 45 from 'ulcer  
of the liver.' **Past history.** He had had the usual childhood  
diseases. In 1898 he had pneumonia without sequelae and  
in 1934 he had acute arthritis of the ankle for 3 months.

**Physical examination.** This showed a rather poorly  
nourished white male who appeared chronically ill. The  
height was 5 ft 6 in and weight was 139 lb (63 kg). He  
had complete adentia, bilateral reduction of hearing,  
moderate emphysema, physical signs indicating an infiltra-  
tive process in the left upper lobe of the lung, rather faint  
heart sounds, poor rectal sphincter tone, a sluggish left  
ankle jerk, an absent right ankle jerk and a spermatocelc.  
Blood pressure, 170 mm Hg systolic, 80 diastolic.

**Laboratory examination.** The blood count showed a  
hemoglobin of 16.3 gm (92% Sahli), a red cell count of 4.5  
million, a total white cell count of 7640 with 75 per cent  
neutrophils. The urine was acid, lemon colored, clear, of  
a specific gravity of 1.024 and free of albumin. The Bene-  
dict test for sugar was 2+. The sediment contained  
rarely a squamous and a white cell. The Wassermann and  
Kahn reactions were negative. The corrected sedimenta-  
tion rate was 34 mm in 1 hour (Wintrobe). There were  
many tubercle bacilli in the sputum. The trend of the  
blood chemistry values during the course of the patient's  
hospitalization is shown by the figures in table 1. The  
liver function tests are recorded in table 2. They did not  
indicate any liver damage.

**Röntgen ray examination.** This showed evidence of an  
inflammatory process with cavitation in the left upper  
lobe extending into both lower lobes, and moderate  
pleural thickening on the left with deviation of the  
mediastinum toward the left.

*Course.* The patient remained in the hospital until his death 7 months later. He had an intermittent low-grade fever during his entire stay, and the tuberculous process gradually spread. On Jan. 25, 1940, a pneumothorax was begun on the left side. This was technically successful and was followed by weekly refills, but the course of the disease was not arrested. Because of the continued advance of the tuberculous process in the right lung, a pneumothorax was also ordered on the right. The initial right pneumothorax was given on May 16, 1940. At this time his condition was critical. He died on May 25, 1940.

TABLE 1. BLOOD CHEMISTRY

| Date    | Blood Sugar, mg. % | Plasma CO <sub>2</sub> Combining Power, vol. % | Serum Cholesterol, mg. % | Blood NaCl, mg. % | Blood Urea, mg. % |
|---------|--------------------|--|--------------------------|-------------------|-------------------|
| 2/ 9/40 | 231                |  | 231                      |                   |                   |
| 2/12/40 | 408                |  | 171                      |                   |                   |
| 2/29/40 | 250                |  |                          | 420               | 15                |
| 3/11/40 | 377                | 62   |                          |                   |                   |
| 4/10/40 | 454                | 63   |                          | 408               |                   |
| 5/16/40 | 384                | 17   |                          | 436               |                   |

The course of the diabetes was not remarkable during the first 3 months of his hospital stay. He was originally given a diet of C 200, P 90, F 110, and 30 u of protamine zinc insulin. On Nov. 3, 1939, 5 days after his admission to the hospital, blood sugar specimens were taken before each meal. The values were 122, 200, and 170 mg. per cent respectively, indicating a type of response characteristic of a fairly well controlled diabetic. Because of persistent mild glycosuria, the dose of insulin was raised on Dec. 2nd to 40 u of protamine zinc insulin and 10 u of amorphous (regular) insulin. The urine remained sugar-free on this regimen for over a month. After this time glycosuria began again and continued despite an increase in the insulin intake to 95 u on Jan. 27, 1940. On Feb. 5th, the diet was changed to C 500, P 90, F 110. This was done because of the increase in insulin sensitivity resulting ordinarily from a high carbohydrate diet (10), and also because of suspected hepatic involvement. On the same date the fasting blood sugar was 280 mg. per cent and the urine showed a 4 + sugar and a 1 + acetone. The insulin intake consisted of 60 u of protamine zinc insulin and 60 u of amorphous insulin.

His course hereafter was most extraordinary. The chief features are portrayed graphically in figure 1. It was recognized that the phenomenon of insulin resistance was present. The insulin dosage was increased rapidly and progressively. On February 12th, the insulin intake was 800 u and the blood sugar was 408 mg. per cent. The quantitative sugar output was 216 gm. per 24 hours and he had a 1 + acetone in the urine. Although continued daily increase of insulin did not show any immediate result, as measured by urinary sugar output, the blood-sugar level over the next 2 weeks gradually diminished to considerably lower levels. On February 23rd the total insulin dosage was 2280 u and the fasting blood sugar was 263 mg. per cent. The urine still showed 4 + sugar and 1 + acetone. The greatest daily intake of insulin during his

entire hospital stay was on February 26th, when he was given 1940 u of unmodified insulin and 520 u of protamine zinc insulin, or a total of 2460 u. During the next 10 days the dosage was gradually lowered because the blood-sugar level and the sugar output in the urine decreased markedly and the acetone disappeared from the urine. At the end of this period clinical symptoms of hypoglycemia developed. On March 6th the fasting blood sugar was 55 mg. per cent. On this day he received a total insulin dosage of 1890 u and on the following day the fasting blood sugar was 52 mg. per cent. At this time it was decided to reduce the insulin dosage drastically (11). On March 10th it had reached a value of 500 u for the total daily dosage. On this day, however, the fasting blood sugar was again markedly elevated, being 377 mg. per cent. The urinary sugar output was 170 gm. per 24 hours. The acetone was 2 +. This attempt to lower the insulin dosage being obviously unsuccessful, the amount was raised in 2 days to 1380 u, on which regimen he was continued to March 31st. A Congo red test for amyloid made on March 28th showed 47 per cent retention of the dye in one hour. During this period the blood-sugar values ranged from 117 to 330 mg. per cent and the average urinary sugar output fluctuated between 72 and 198 gm. per 24 hours. The urine was free of acetone. It may be noted that the output of sugar was considerable and that the blood-sugar level still averaged around 250 mg. per cent. Clinically, the patient did not feel nearly so well as he had before this. Several times during the day and night he perspired, had symptoms suggesting hypoglycemia, and was generally uncomfortable. The daily insulin dosage was therefore further decreased to 920 u (420 u of unmodified insulin and 500 u of protamine zinc insulin). This was continued until May 20th. Throughout this period the blood-sugar level was higher, the fasting values

TABLE 2. LIVER FUNCTION TESTS

|  |   |
|--|---|
| Retention of bromsulphalein:             | $\frac{1}{2}$ hr., 0<br>1 hr., 0                      |
| Retention of galactose: <sup>1</sup>     | 1 hr., 31 mg. %<br>$1\frac{1}{4}$ hr., 18 mg. %       |
| Synthesis of hippuric acid: <sup>2</sup> | 4.8 gm. found in 1000 cc urine.<br>(Normal 3-3.5 gm.) |

<sup>1</sup> Determined through the courtesy of Dr. T. L. Althausen.  
<sup>2</sup> Determined through the courtesy of Dr. D. K. Burnham.

ranging from 350 to 483 mg. per cent. The urinary glucose output varied from 234 to 402 gm. per 24 hours. Acetone, and later diacetic acid, reappeared in the urine. However, the patient felt more comfortable than he had at any time during his period of insulin resistance. Because of increased formation of diacetic acid, the insulin dosage was increased from 1220 u on May 21st to 2200 u on May 24th. Fifteen hundred gm. of glucose was given during this day. The acetone and the diacetic acid disappeared from the urine, but clinical signs of diabetic coma progressed and the patient died in the evening of May 25th, 1940.

*Summary of pathological findings* (Dr. A. J. Cox). The autopsy, performed 16 hours after death, showed bilateral pulmonary tuberculosis, with a large cavity six cm. in diameter in the upper lobe of the left lung and many small

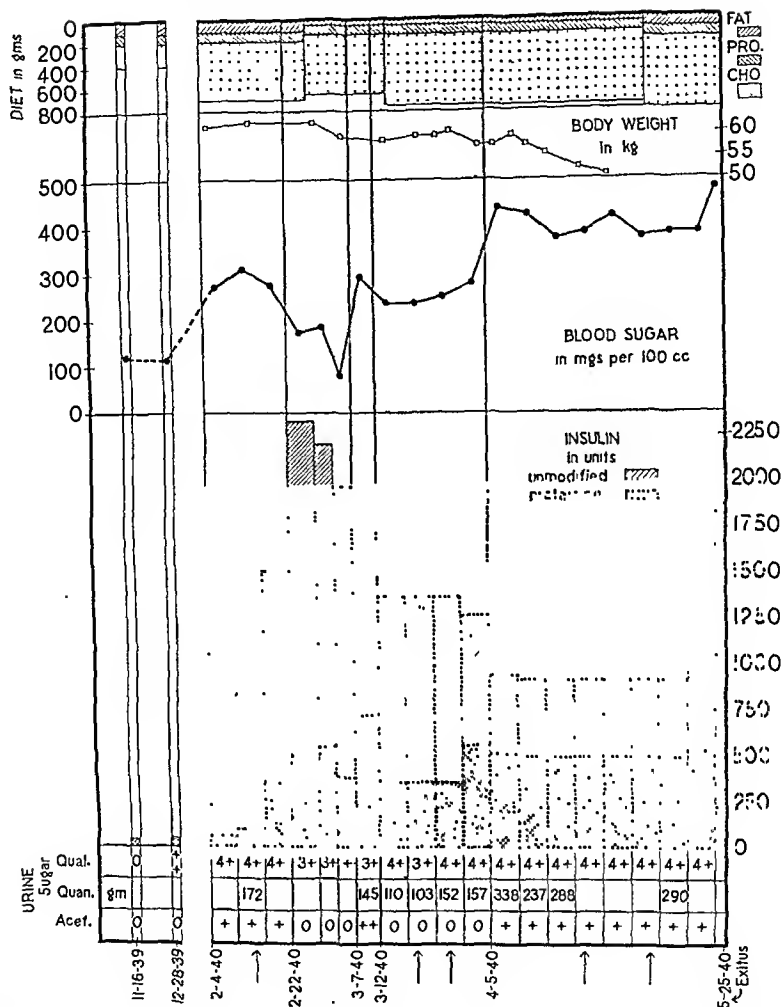


Fig 1. DATA OBTAINED DURING PATIENT'S HOSPITALIZATION. The detached portion to the left represents the period before hospitalization. The dates on the right indicate the dates on which the experiments were made.

nodules throughout the remainder of this lung as well as the upper lobe of the right lung. The right middle and lower lobes showed only an occasional small tubercle. A few tubercles were present in the moderately enlarged hilar lymph nodes, but no gross caseation was seen. Histologically, the cavity and many tubercles were surrounded by moderate amounts of fibrous tissue, indicating

that they were not rapidly progressing lesions, but some of the nodules were not so demarcated.

The pancreas was 20 cm. long and its cross-section measured 1 by 3 cm. at the head. However, the body and tail were much thinner, and it was thought that the organ as a whole was distinctly smaller than normal. The markings on the cut surface were normal, as was the histo-

logical appearance of sections stained with hematoxylin-eosin, although islets of Langerhans were not numerous. The adrenals, testes, and prostate showed no significant gross or microscopic changes. The thyroid gland, although not enlarged, showed distinct evidence of hyperplasia. Its follicles varied considerably in size. In many follicles there was practically no colloid; in others the colloid was faintly stained and showed marked peripheral vacuolation. The lining epithelium was columnar in many places and many of the nuclei had unusually deeply stained chromatin. No mitotic figures could be identified with certainty. There was no lymphoid tissue in the organ. The anterior lobe of the hypophysis contained eosinophilic and basophilic cells in approximately normal numbers. A moderate number of small basophilic cells extended into the posterior lobe in one region. The remaining basophils were normal. Many contained fairly large cytoplasmic vacuoles. Many of the eosinophils were also vacuolated, but most of the vacuoles were smaller than those in the basophils and they were often multiple. In the capsule of the gland in one region were several long rows of small cells with scanty cytoplasm. The arrangement of these cells suggested that they were epithelial, but their identity could not be established. There was a slight diffuse increase in the interstitial connective tissue of the anterior lobe in places, and toward the center of the lobe was a small dense scar. However, the amount of reduction of the number of epithelial cells on this account was negligible.

The liver was enlarged, weighing 2700 gm. It was firm and pale brown. Its vessels were normal. The cut surface was uniform and slightly opaque, with no visible lobule markings. A little thick turbid blood-tinged fluid could be expressed from the cut surface. Lugol's solution stained the liver tissue deep mahogany brown, and the exuding thick fluid was similarly stained. Further tests on aqueous extracts of the liver substance showed large amounts of a substance which in solution was milky white, opalescent, and had many of the properties of glycogen. It could be precipitated by alcohol but not by heat or trichloroacetic acid, and it disappeared on acid hydrolysis, yielding a substance which would reduce Benedict's solution. Although no quantitative determinations were made, the substance remained in apparently undiminished quantity in specimens of the liver stored in the ice box for 2 weeks. Similarly, incubation of pieces of liver for 4 days at 37° C. did not destroy it, whereas incubation with ground liver obtained from another autopsied body resulted in disappearance of the substance within 24 hours. Histological study showed marked enlargement of the liver cells, some of which had nearly twice the normal diameter. Most of the sinusoids were collapsed. The nuclei of the large cells were normal but the cytoplasm was practically unstained except for a thin rim at the cell margins. Best's carmine stain showed abundant masses of glycogen in these cells. No amyloid was present. No glycogen was demonstrable in any other organs.

The spleen weighed 240 gm. Its pulp was firm and dark red. The heart weighed 230 gm. and appeared normal. No glycogen could be demonstrated in the muscle either by gross iodine test or by using Best's carmine stain on alcohol-fixed tissue, although many of the muscle fibers contained fine vacuoles. There was relatively little arterio-

sclerosis, the most marked lesions being in the descending aorta, where, near the bifurcation, were several scattered medium-sized slightly raised intimal plaques without ulceration or gross calcification. The kidneys were normal. No abnormalities were found in the brain.

#### COMMENT

This case represents an example of insulin resistance which began fairly abruptly in a patient whose diabetes had been quite well controlled during the preceding 3 months.

The course of the patient after he became resistant to insulin may be divided into 5 periods according to the amount of insulin he received. The lines running vertically through figure 1 mark these off abruptly into the following periods: *a*), rapidly increasing insulin requirement; *b*), peak dosage; *c*), low dosage; *d*), higher plateau; *e*), lower plateau.

The most striking feature of the case is the fact, best gleaned from the composite chart, that the average fasting blood sugar, the glycosuria and the ketonuria were almost inversely proportional to the insulin dosage. In other words, the response to insulin was much like that of the ordinary diabetic except that huge doses of insulin were necessary to produce a glucose-lowering effect in the blood.

The case was studied carefully to rule out various factors which have been thought to play a rôle in insulin resistance. The effect of diet did not seem to be important. Shortly after the beginning of the resistant stage, the carbohydrate intake was raised to 500 gm. a day. Thereafter the scheduled diet contained 500 to 600 gm. daily. The patient often left some of this on the tray, probably enough to affect the individual blood sugar values but not enough to affect the averages. The fat intake varied from 40 to 100 gm. a day. It was thought that the higher fat intake was associated with greater ketonuria.

There was no clinical evidence of allergy. In comparison to the amount of protein-containing solution, the tissue reactions were slight.

Since sources of insulin may have a bearing on the problem of insensitivity several brands were employed, including amorphous or 'regular' insulin (beef, pork and sheep)<sup>2</sup> and solution of zinc insulin crystals and protamine zinc insulin.<sup>3</sup> No difference in effect was noted.

#### INVESTIGATIVE STUDIES

Houssay (5) has shown that injections of the anterior lobe of the pituitary gland into dogs produces a temporary diabetic state. More recent work by Jensen (12), Young (13), and others has suggested

<sup>2</sup> The various brands of regular insulin used were manufactured by Eli Lilly Co., Indianapolis, Ind., Sharpe and Dohme Co., Philadelphia, Pa., and Frederick Stearns & Co., Detroit, Mich.

<sup>3</sup> The solution of zinc insulin crystals and the protamine zinc insulin used were manufactured by Eli Lilly Co., Indianapolis, Ind.

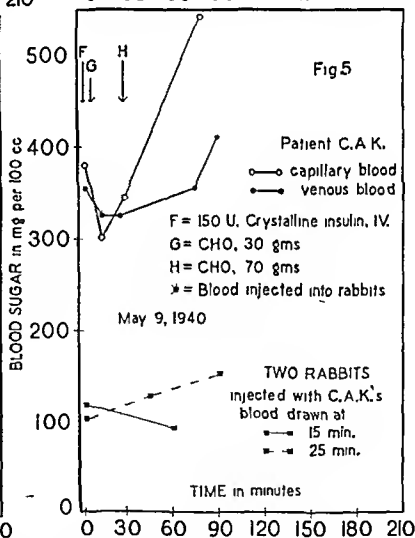
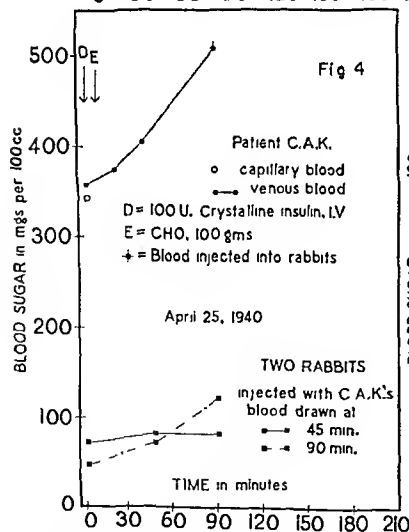
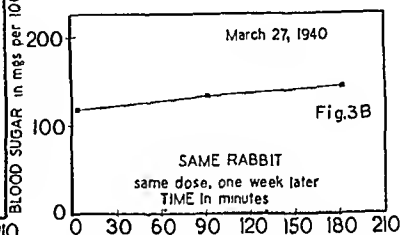
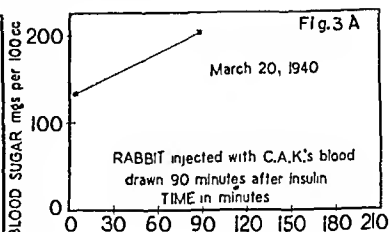
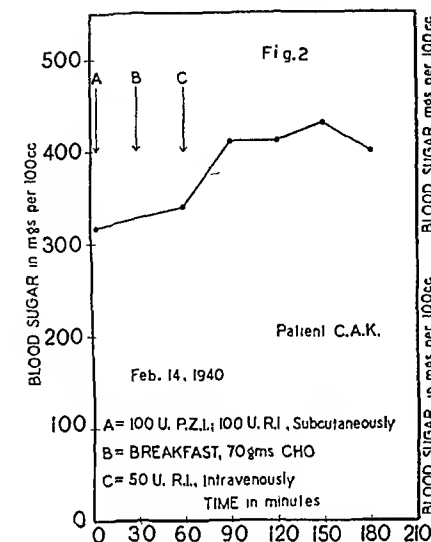


Fig. 2. INSULIN-CARBOHYDRATE TOLERANCE test illustrating continued rise of blood sugar despite repeated large doses of insulin.  
Fig. 3. Rise in blood sugar of a rabbit after injection of blood from the patient despite previous injection of 120 u of amorphous insulin subcutaneously into patient.

Fig. 4. Unusual response of two rabbits injected with blood from patient C.A.K. after a large dose.

ills.

that the ability to utilize carbohydrate is inherent in the tissues and that this utilization is facilitated by insulin and retarded by factors secreted by the anterior lobe of the pituitary gland. Young separated the pituitary 'antagonist' into two parts. The first of these, which he called the 'glycotropic' factor, antagonized the action of insulin although it did not produce hyperglycemia or diabetes when injected into the normal animal. The second, which he termed 'diabetogenic,' also antagonized insulin but in addition produced hyperglycemia, glycosuria, and ketosis. Continuation of its injection led to permanent diabetes.

In the study of this patient during the period of his manifested insulin insensitivity, two methods of investigative procedure were used. The first was the study of the response of the patient's blood sugar to subcutaneous and intravenous insulin; the other was the response of a rabbit's blood sugar after intraperitoneal injection of blood specimens from the patient under these circumstances.

*Experiment 1*<sup>1</sup> (fig. 2). On Feb. 14, 1940, the fasting blood sugar was 316 mg. per cent. At this time he was given 100 u of amorphous insulin and 100 u of protamine zinc insulin. One-half hour later he ate a light breakfast containing about 70 gm. of carbohydrate. After another half-hour the blood sugar was 341 mg. per cent. He was then given 50 u of amorphous insulin, intravenously. The values of the glucose content of the blood samples taken at half-hour intervals after this were as follows:

|              |     |     |     |     |
|--------------|-----|-----|-----|-----|
| Hours        | .5  | 1   | 1.5 | 2   |
| Mg. per cent | 411 | 411 | 429 | 400 |

This experiment demonstrates that there was no lowering of the blood sugar by either 100 u of amorphous insulin given subcutaneously or 50 u given intravenously. The rise of the blood sugar proceeded much as one might expect after a meal without the benefit of insulin administration. The possibility of an immediate and transient fall cannot be denied but the occurrence of a progressive rise after such a large dose of intravenous insulin suggests the absence of any insulin effect.

*Experiment 2.* On March 20th the value of the fasting blood sugar was 117 mg. per cent for the venous blood and 113 mg. per cent for the capillary blood obtained by finger puncture. The patient was given 120 u of amorphous insulin and 120 u of protamine zinc insulin, subcutaneously. One and one-half hours later 10 cc. of venous blood were withdrawn and injected immediately into the peritoneal cavity of a 2-kg. rabbit kept in a fasting condition. The rabbit's fasting blood sugar just before the injection was 133 mg. per cent (fig. 3, a). One and one-half hours later

its blood sugar had risen to 210 mg. per cent. Thus the blood transferred from the patient 1.5 hours after 120 u of amorphous insulin conveyed to the rabbit no factor for utilizing sugar but actually the blood had a hyperglycemic effect.

*Experiment 3.* On March 27th the experiment was repeated in a slightly modified form. The patient's fasting blood sugar was 246 mg. per cent and the rabbit's fasting blood sugar was 117 mg. per cent. An intraperitoneal transfer of 10 cc. of blood withdrawn from the patient 1.5 hours after he had received 120 u of amorphous insulin and 120 u of protamine zinc insulin yielded, in the rabbit, a blood sugar of 132 mg. per cent 1.5 hours after injection, and a value of 142 mg. per cent 3 hours later (fig. 3, b).

Although the curve changes only slightly from the initial value, the important fact is that it rises instead of falling. Such a rise has been said to occur in rabbits anyway (although we have been unable to find any such report in the literature). If this be true, the phenomenon remains remarkable until it is explained. The explanation we postulate is the existence of a diabetogenic factor. It is of interest that the rise in the rabbit's blood sugar was greater in *experiment 2*, at the time of which the patient's blood sugar was lower (i.e., insulin effect was more pronounced). Confirmation of this is offered in *experiment 4* and 5.

*Experiment 4.* On April 25th the patient was given 100 u of crystalline insulin intravenously while in a fasting condition. Five minutes later he ate a breakfast containing approximately 100 gm. of carbohydrate. Blood samples were then withdrawn at intervals measured from the time of injection of insulin. The blood sugar values were as follows (fig. 4, top):

|              |     |     |     |     |
|--------------|-----|-----|-----|-----|
| Minutes      | 0   | 20  | 45  | 90  |
| Mg. per cent | 356 | 375 | 405 | 515 |

When blood was taken for chemical analysis at 45 and at 90 minutes, an additional 10 cc. was withdrawn for immediate injection into the peritoneal cavity of a rabbit. The blood sugar values were as follows (see fig. 4, bottom):

|   |     |     |     |
|---|-----|-----|-----|
| Minutes after injection into rabbit   | F   | 45  | 90  |
| Mg. per cent first rabbit, injected with 10 cc. of patient's blood drawn 45 minutes after insulin     | 121 | 128 | 129 |
| Mg. per cent in second rabbit, injected with 10 cc. of patient's blood drawn 90 minutes after insulin | 97  | 121 | 173 |

Incidentally, the patient's initial capillary blood sugar was 346 mg. per cent when his venous blood sugar was 356 mg. per cent; the difference may merely be within the accuracy of the chemical technique; nevertheless, this is commented upon because the arterial is lower than the venous value, instead of higher, as is usually expected. This phenomenon also occurred in *experiment 2*. Griffiths (14) found that in

<sup>1</sup> Dr. W. C. Cutting aided in the preparation of these experiments.

young and old diabetics alike the arteriovenous blood sugar difference was smaller than in the normal individual. He called attention to the frequent occurrence of negative arteriovenous differences in the diabetic and its rarity in the normal individual but could offer no explanation. The rabbit experiments demonstrate that, 45 to 90 minutes after a large intravenous dose of insulin, this patient's blood, when transferred to rabbits, not only failed to lower the rabbit's blood sugar, but, on the contrary, caused it to rise. We see in this a hyperglycemic factor. This substance may have developed before the collection of the 45 minute specimen, but sufficient quantity for demonstration was found only after a longer interval. On the other hand an 'anti insulin' or 'glycotropic' effect was already present at 45 minutes. This suggests the possibility of the separate identity of the anti insulin and hyperglycemic factors.

**Experiment 5** On May 9th the last experiment was repeated, with certain changes. First, the comparative capillary and venous blood sugar values of the patient were studied over a longer period, i.e., 15 hours after 150 u of crystalline insulin had been injected intravenously (fig 5, top), second, the effect of the injection of 10 cc of venous blood into rabbits was observed when drawn at shorter intervals, i.e., 15 and 25 minutes after the insulin injection into the patient (fig 5, bottom).

The blood sugar curves obtained were as follows

| Time in minutes            | F   | 15  | 25  | 70  | 80  | 90  |
|----------------------------|-----|-----|-----|-----|-----|-----|
| Blood sugar in mg per cent |     |     |     |     |     |     |
| Venous                     | 405 | 375 | 374 | 405 |     | 455 |
| Capillary                  | 430 | 350 | 396 |     | 545 |     |

The blood sugar values of the rabbits were as follows

| Minutes after injection into rabbit   | F   | 45  | 60 | 90  |
|---|-----|-----|----|-----|
| Mg per cent in first rabbit, injected with 10 cc of patient's blood drawn 15 minutes after insulin  | 117 |     | 87 |     |
| Mg per cent in second rabbit, injected with 10 cc of patient's blood drawn 25 minutes after insulin | 101 | 132 |    | 151 |

The findings of this experiment further support the conclusions reached in the preceding experiments. Again there was an absence of the expected positive arteriovenous difference occurring after the ingestion of food and a dose of insulin (fig 5, drop in open circle lines).

This time the intravenous administration of a large dose of insulin given in conjunction with only a small carbohydrate meal (fig 5, G) did produce a depression of the blood sugar level which lasted for about 70 minutes.

The rabbit experiments can best be interpreted to signify that 15 minutes after the intravenous administration of a large dose of insulin into the patient (fig 5, F), enough active insulin was contained in it to lower the blood sugar of the rabbit. This was the sole instance in our experiments in which the transfer produced the anticipated sugar-utilizing effect. Ten minutes later (fig 5, second asterisk), with the level of the patient's blood sugar quite unchanged, no demonstrable insulin effect on the second rabbit could be shown (fig 5, dash dot line). In addition, this finding lends further support to the contention that the glycotropic factor present in this patient's blood was a substance completely separate from insulin. One may speculate whether this factor was present, temporarily depressed in its action by large amounts of insulin, or whether it was the result of a hypothetical insulin inactivator or antagonist in the patient.

#### DISCUSSION

The investigative studies on this patient were originally undertaken in an effort to study the effect of insulin on the blood sugar of the patient and to demonstrate the presence of insulin in the blood of the patient after injection. It has been stated (15) that 2 to 4 u of insulin will produce shock in a rabbit and that about one third of a u is necessary to produce a certain blood sugar lowering effect. If one were to assume the patient's blood volume to be 6000 cc, it would appear that in the rabbit experiments there should have been one fifth u or more in each sample removed for animal inoculation, were the insulin still present in an active form 15 to 90 minutes after its injection into the patient. However, if one grants that within a few minutes insulin diffuses throughout the interstitial fluid, the dilution factor should be in the neighborhood of 18 liters, this would mean that about 1/15 of a unit would be contained in each transfer. This amount seems hardly sufficient to produce any lowering of the blood sugar of the rabbits, and in fact, in only one instance did any such depression occur. On the contrary, the blood sugar values were usually higher. In general, the rise appeared to become more marked as the time interval after the injection of insulin into the patient increased. These results offer confirmation of Glen and Eaton's findings (8) that the injection of the serum of their insulin resistant patient into rabbits induced an active insulin antagonism in them and that this was more marked if the patient had had insulin one half hour before withdrawing the blood.

De Wesselow and Griffiths (16) injected the plasma of certain elderly diabetics into rabbits and found that the duration of the hypoglycemia produced by intravenous insulin was reduced whereas the blood of young diabetics had no such effect. This suggested



that the ability to utilize carbohydrate is inherent in the tissues and that this utilization is facilitated by insulin and retarded by factors secreted by the anterior lobe of the pituitary gland. Young separated the pituitary 'antagonist' into two parts. The first of these, which he called the 'glycotropic' factor, antagonized the action of insulin although it did not produce hyperglycemia or diabetes when injected into the normal animal. The second, which he termed 'diabetogenic,' also antagonized insulin but in addition produced hyperglycemia, glycosuria, and ketosis. Continuation of its injection led to permanent diabetes.

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*Experiment 4.* On April 25th the patient was given 100 u of crystalline insulin intravenously while in a fasting condition. Five minutes later he ate a breakfast containing approximately 100 gm. of carbohydrate. Blood samples were then withdrawn at intervals measured from the time of injection of insulin. The blood sugar values were as follows (fig. 4, top):

|              |     |     |     |     |
|--------------|-----|-----|-----|-----|
| Minutes      | 0   | 20  | 45  | 90  |
| Mg. per cent | 356 | 375 | 405 | 515 |

When blood was taken for chemical analysis at 45 and at 90 minutes, an additional 10 cc. was withdrawn for immediate injection into the peritoneal cavity of a rabbit. The blood sugar values were as follows (see fig. 4, bottom):

|   |     |     |     |
|---|-----|-----|-----|
| Minutes after injection into rabbit     | F   | 45  | 90  |
| Mg. per cent first rabbit, injected     |     |     |     |
| with 10 cc. of patient's blood drawn    |     |     |     |
| 45 minutes after insulin                | 121 | 128 | 129 |
| Mg. per cent in second rabbit, injected |     |     |     |
| with 10 cc. of patient's blood          |     |     |     |
| drawn 90 minutes after insulin          | 97  | 121 | 173 |

Incidentally, the patient's initial capillary blood sugar was 346 mg. per cent when his venous blood sugar was 356 mg. per cent; the difference may merely be within the accuracy of the chemical technique; nevertheless, this is commented upon because the arterial is lower than the venous value, instead of higher, as is usually expected. This phenomenon also occurred in *experiment 2*. Griffiths (14) found that in

<sup>4</sup> Dr. W. C. Cutting aided in the preparation of these experiments.

# Combined Use of Testosterone Propionate and Psychotherapy in Treatment of Hypogonadal Behavior-Problem Boys

## [[Treatment of Hypogonadism]]

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THE CLOSE relationship between the endocrine system and neuropsychiatric functions is becoming more and more recognized. The evidence pointing to this interrelation has been accumulating from many sources. Thus, anatomical (1), biochemical (2), psychological (3), neuropathological (4) and clinical studies (5-7) have all played a part. The observation by Rowe (8) that approximately 75 per cent of 374 problem children disclosed definite evidence of pituitary defect represents one of the most exhaustive clinical studies bearing upon the problem.

The frequent occurrence of endocrinopathy and misbehavior in children may indicate that a common genetic factor is responsible for both the physical and mental aberrations. Personal observation, however, has led to the impression that the problem behavior of many endocrinopathic children like the misbehavior of the normally constituted child is frequently experientially determined. Such a child, because of his somatic disfigurement becomes the target of jibes and excoriating epithets inflicted by other children and even by childishly humored adults. Reactions of depression or compensatory aggressions soon follow.

While psychotherapy is undoubtedly helpful for the adjustment of such patients it naturally fails in itself to alter the bodily defects which initiated the series of experiences responsible for the reactions. The proper use of endocrine preparations, therefore, becomes important. This is particularly true in generally hypoplastic boys since the synthetically prepared male sex hormone, testosterone propionate, has now become available in sufficiently pure form and in sufficient quantities for clinical use.

The following case reports will disclose the problems encountered and the results obtained in a series of such hypogonadal problem children.

### CASE REPORTS

Case 1, S K, a white male 12 years and 9 months of age presented a typical dystrophia-adiposa genital syndrome with characteristic shoulder-pelvic girdle adiposity and infantile genitalia. The penis was 2 cm. in length. The parents complained of the child's misbehavior in school. He frequently interrupted the teacher's remarks in order to correct what he considered to be erroneous statements and he insisted on calling out the answers to questions directed to other children.

He was mentally alert, very boastful and spoke of his intellectual superiority over other children. He never cried about his genital abnormality nor was he overemotional in other respects. But he refused to undress in the gymnasium and to enter in the nude the swimming pool at school. On the Binet-Simon test he displayed a mental age of 18 years 3 months and an intelligence quotient of 143.

Here we were dealing with a mentally precocious child with dysplastic constitution whose judgment, still in keeping with his chronological age, permitted him to flaunt his mental superiority before his class-mates. As a result he became the shunned member of his class. Left to himself he became more egocentric and self-sufficient.

He was treated with anterior pituitary extract<sup>1</sup> twice weekly, and placed on dietary restriction. Although he lost weight with this treatment, at the end of 2 months the genitals had failed to develop. He was, therefore, given additional subcutaneous injections of testosterone propionate twice weekly in doses of 25 mg. for the first month, 10 mg. twice weekly during the 2nd month and 5 mg. (each injection) thereafter. Psychotherapy by way of persuasion and reeducation in order to improve his personality traits and social relations was also included. Only after 9 months of such treatment when the bodily form approached the normal and the penis had grown to a length of 5 cm. with a circumference of 6 cm. did he make a satisfactory adjustment toward his work and play fellows. He then saw and accepted his previous forwardness and conceit in school as an overcompensation for his feelings of inferiority to other children.

<sup>1</sup> The anterior pituitary extract was supplied by E. R. Squibb and Sons, New Brunswick, New Jersey.

*Case 2, M.S.*, a white male 14 years of age also presented the syndrome of dystrophia-adiposo-genitalis. The penis was 2 cm. in length and 4 cm. in circumference. In addition, the testes were bilaterally undescended. These, however, could be palpated in the inguinal canals. Unlike the previous patient, he was slow in action, shy and retiring, and refrained from all games with other boys. His mental age (Binet-Simon) was 12 years; the intelligence quotient was 86 and the B.M.R.  $-15$ . Thyroid 1 grain, twice a day soon raised the B.M.R. to  $-8$ . Testosterone propionate,<sup>2</sup> 10 mg. twice weekly, injected subcutaneously over a period of 3 months resulted in more normal bodily configuration, a penile development to 5 cm. in length and 6 cm. in circumference with bilateral descent of the testes. In addition, he became more alert mentally and advanced on the Binet-Simon scale to an I.Q. of 98 (mental age 14 yr., 1 month). His attitude toward other children improved so that he spontaneously engaged in combative sports with the boys of the neighborhood.

*Case 3, D.B.*, an 11-year-old white male was seen in June, 1938, because of disrespect, moodiness, temper tantrums and frequent fights with other children. These complaints dated back about 2 years, prior to which time he had been quiet and had seemed almost too well behaved. He made very good marks in school but here, too, he had become talkative and boastful. The patient spent a good deal of time with his mother and as an only child had been pampered. The first indication of behavioral change had occurred when the mother, as was her usual custom, attempted to bathe him. He refused to expose himself before her and in response to her insistence gave way to an outburst of temper which for him was something new. This was followed by a crying spell.

Physical examination disclosed a normal height (56.7 in.) but a weight of 110 lb. which was about 31 lb. above the maximum normal of 79.4 lb. (9). There was no skeletal disproportion. The fat deposition was of the shoulder-pelvic-girdle type. The breasts were also obese but disclosed no evidence of mammary tissue. The genitalia were diminutive. The left testis had descended but the right testis was still in the inguinal canal and could not be pushed into the scrotum. Each testis was about the size of a small filbert nut. The penis was infantile in appearance being only 1.5 cm. in length. Neurological findings were essentially normal but the right cremasteric reflex was absent. B.M.R. was  $-19$ . The results of other laboratory studies were normal. Mentally the child was alert, spoke relevantly, was well behaved and co-operative. He could not explain why he mishaved and when asked if it might be because he wanted something which he did not possess he replied that he had everything and even boasted of his superiority over other boys. Binet-Simon test revealed a mental age of 12 years 7 months and an I.Q. of 114.

Treatment consisted of a diet containing 1533 calories, an amount which was based on a body weight of 70 lb. It consisted of protein 65 gm., carbohydrate 127 gm. and fat

85 gm.; thyroid, .5 grain 3 times a day adequate vitamin intake; testosterone propionate, 5 mg. twice weekly by subcutaneous injection. In addition, psychotherapeutic discussions elicited that he was painfully aware of his genital inferiority, having made comparisons with other boys. His aggressiveness was merely to show these other boys that he could still be their superior. His recent recognition of his own difference from other boys was responsible for his sudden reluctance at disrobing before his mother. His temper outburst was his substitute for a more active form of aggression. By the end of November, 1938, after 5 months of treatment he showed an excellent physical change. The penis had grown to 3 cm., the height had become 58.3 inches (a growth of 1.6 in.) and the weight was reduced to 102 lb. (a reduction of 8 lb.). The most striking result however was observed in his behavior. He again became the 'good boy' at home although he remained adamant in his refusal to permit bathing by his mother. The fighting had stopped but wrestling became his favorite sport. Treatment was discontinued. Three months later his behavior was still satisfactory. Figure 1 shows a comparison of the genitals before treatment and 3 months after cessation of treatment.

*Case 4, H.S.*, a white male 14 years and 1 month of age, was referred in November, 1938, because he 'acted peculiarly' at home. This peculiar behavior dated from the death of his father 2 years previously. At that time he went to live in the home of an older boy cousin who discovered that the patient had small genitals and taunted him about it. This so shamed him that he avoided other children whenever he could. He had frequent periods of sadness which were brought on either by thoughts of his deceased father or if he argued with his uncle with whom he lived. He felt that the uncle was taking advantage of him and his mother. Because he was now aware of his own defects, he felt that he would never be able to do anything about his uncle's unfairness, especially since he felt that he would always remain 'weak and boyish.' The difficulty concerning the uncle was found to have arisen from the patient's impression that the business affairs of his mother were being mishandled by the uncle. The mother, however, did not corroborate this accusation. At home the patient always wished to remain alone, although by his own admission he liked to listen in on the conversation of others from an adjoining room where he was supposedly studying.

Physically he was of normal height, 59.3 inches (normal range, 58.6-62.8 in.) and weighed 110 lb. (normal range 81.1-102.9 lb.). His lower bodily measurement of 30.8 in. was 2.3 in. longer than his upper measurement of 28.5 in. Normally, this difference should have been about 1 in. He disclosed a moderate obesity of the shoulder-pelvic-girdle type, a penis 1.5 cm. in length, very small testes which, however, were well descended in the scrotum. The findings in a neurological examination were normal. Psychiatric survey disclosed a shut-in type of personality with marked feelings of resentment against his cousin for teasing him and against his uncle whom he considered a cheat. The results of all of the laboratory studies made were normal. Binet-Simon test disclosed a mental age of 16 yr. and an I.Q. of 113.

<sup>2</sup> The author acknowledges with appreciation the aid of the Ciba Pharmaceutical Products Company Inc. for supplying the testosterone propionate (Perandren) and for partially defraying the expense of these studies.

Treatment consisted of subcutaneous injections of testosterone propionate 3 times weekly. This was given consecutively in doses of 5 mg. for 3 injections, 10 mg. for 5 injections, 25 mg. for 7 injections, 10 mg. for 5 injections, and 5 mg. each for the remaining 10 injections. During these 10 weeks the patient was also treated psychotherapeutically. He could reason very well so that he could readily be made to see the inadequate basis for his suspicion of his uncle. He soon stated that he had placed his uncle in the same category as the uncle's son, i.e., the cousin who had made him so painfully aware of genital inferiority. As the phallus developed it was easy for him to accept the jibings of his cousin as manifestations of a childish sense of humor. By this time the height had become 60.2 inches (an increase of 0.9) and the weight was reduced to 105 lb. (loss of 5 lb.). The penis had grown to 6.5 cm. in length and 8 cm. in circumference. A crines pubis made its appearance. Treatment was discontinued. Three months later a communication from his mother disclosed that 'his behavior has changed more than I can tell you. He used to be moody and very distant. It would take him a very long while to make friends. He has become more forward and acts more as if he were on the same footing with others. He was always kind but now he seems more than ever to take up for the underdog.' Figure 2 shows the genital changes in this patient.

**Case 5, P.S.**, a white male, 11 years and 10 months of age was referred in March, 1941, because of peculiar motions of his mouth, vicious temper, stinginess and rudeness. The boy's father had deserted the mother 3.5 years previously. About 1.5 years ago the child learned of his mother's intention to remarry. Soon thereafter he began displaying various tics. At the time of his first visit, he twitched his mouth and evoked a peculiar expiratory grunt. He cried easily and bragged a good bit about his cleverness, particularly regarding matters of money. He refused to spend his own money and spoke of its great accumulation as the goal toward which to strive. He took a delight in teasing his mother and frequently made remarks in the presence of her second husband threatening to tell him of some secret about her. The mother had found it very difficult to discipline the child since he took advantage of their congested living quarters and cried so loudly at the least provocation that the landlord who lived just below them threatened to make them move. The mother would then yield to his demands.

Examination disclosed a well grown boy whose height of 59.7 in. was 0.9 in. taller than the maximal normal of 58.8 in. for his age. The weight was 115.8 lb. about 17 lb. above the maximum normal of 99 lb. for the height. The skeleton showed a eunuchoid disproportion, the upper measurement being 28.1 in. as compared to a lower measurement of 31.6 in. The genitalia were extremely small. The penis was 1 cm. in length, the right testis was palpable in the diminutive scrotum but it was also tiny. The left testis could not be felt in the scrotum or inguinal canal. Neurological examination merely disclosed numerous repeated, stereotyped and imitable twitching movements of the lips with occasional expiratory grunting. These could be controlled by persuasion. No evidence of organic neurological defect was noted. Mental survey

disclosed a personality of selfish, bullying, argumentative make-up. While cowardly in the presence of other boys, he was disrespectful and threatening when alone with his mother. He complained that other boys did not like him and when asked why he replied 'Because I'm different.' When asked to explain further he placed the difference on the basis of religion. The mental age was 13 yr. and 4 months and the I.Q. was 112. Basal metabolic rate was -17. The results of all other laboratory studies made were normal. Only once did he allude to a feeling of having been cheated. By this he meant his father's desertion and his sense of being different from others. He would not elaborate on the latter, but because he would never understand before other boys it was assumed that his awareness of a difference had a basis in other than mere religion.

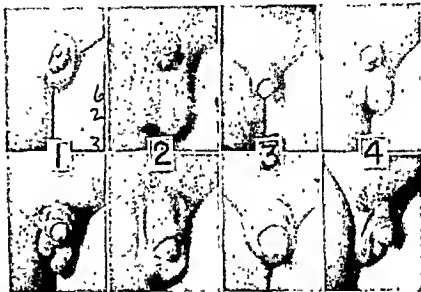


Fig. 1. Case 3, D.B., 11 YEARS OLD; upper, June 1938; lower, Feb. 1939, 3 months after cessation of testosterone propionate therapy for 5 months.

Fig. 2. Case 4, H.S., 14 YEARS OLD; upper, Nov. 1938; lower, Feb. 1939, after 10 weeks of therapy with testosterone propionate.

Fig. 3. Case 7, N.M., 11 YEARS OLD; upper, Dec. 1938, lower, March 1939, after 10 weeks of therapy with testosterone propionate.

Fig. 4. Case 8, D.L., 14 YEARS OLD; upper, Dec. 1938, lower, March 1939, after 3 months of treatment with testosterone propionate.

Here we were dealing with a boy whose obvious resentment toward his mother's remarriage was manifested by temper tantrums, growing disrespect, and threats to expose her as an attempt to embarrass her. Therapeutically however, not only did the boy require attention but the home situation called for radical revision. Accordingly, treatment was directed toward discussion with the parents concerning the establishment of a more uniform attitude. The mother was urged to consider her son just another human being and to be guided in her response to his insults as she would to a stranger's. For example, when asked what she would do if a strange child spoke to her as her own child did, she immediately responded that she would 'cut him cold.' That same attitude of aloofness until the child spoke to her with the respect which he had previously displayed was therefore decided upon. It is interesting that the patient and step-father got along well together, perhaps because the latter did little to discipline the boy.

His allowance thereafter was to be earned on the basis of proper execution of assigned tasks rather than to be received as an expected and outright donation. Discussion was carried on with the patient in order to build up a feeling of security and appreciation. Past grievances which he held against his mother were discussed and dispelled. At the same time subcutaneous injections of testosterone propionate were given twice weekly in 25 mg. doses for the first 12 treatments. For the next 9 weeks the dosage was decreased to 5 mg. each. By that time the genitals had shown excellent growth and both testes became lodged in the scrotum. But most important, his behavior had improved. He was therefore discharged. When seen 2 months later there were no complaints from either parent or child. He had become more obedient, was more respectful, said he felt 'more like a man,' and had developed a genuine feeling of security. He no longer considered himself as having been cheated. The tics had disappeared.

*Case 6, R.M.*, white male 16 years of age, was seen because, according to his mother, he was thin, very shy, had a squeaky voice and seemed otherwise to be effeminate. These complaints dated from about 2 years previously. Prior to that time he had been apparently normal. He was a good student, in the last year of high school. He had always been interested in boys' activities and had been fond of hiking. Recently, however, he avoided more and more the swimming and gymnasium classes in school. As a matter of fact he, very early in the interview, asked if a note would not be written to the gymnasium instructor requesting that he be relieved from this course. At first he gave as an excuse for this request that he felt weak. Somewhat later he mentioned his self-consciousness and feelings of inferiority because of his being different from other children.

Physical examination disclosed a lad of normal stature (62.3 in.) who weighed but 83 lb. (minimum normal for his age was 91.6 lb.). The skeleton was disproportionate, being 28.5 and 33.7 in. for the upper and lower measurements, respectively. The skin was sallow and the face was hairless. The genitals were rather small, the penis being 6 cm. in length and 4 cm. in circumference. The testes were about the size of pigeon eggs but were well descended into the scrotum. A slight crines of the feminine type was present. Findings in the neurological examination were normal. Mental survey disclosed a marked dependence upon his mother with a desire for attention so frequently seen in early childhood. The B.M.R. was -27. All other laboratory findings were normal. On the Binet-Simon test he showed a mental age of 17 yr and 4.5 months and an I.Q. of 111.

The treatment consisted of injections twice weekly of testosterone propionate, 25 mg., for 16 weeks. By this time the penis had grown to 8 cm. in length, the crines had become masculine in type, and the voice had become deeper. He now was more talkative and once again was active in hiking parties; he lost his shyness and re-entered the gymnasium class. At home his attitude toward his mother and sister became more sympathetic and more like that of a mature person. In contrast to previous behavior he no longer permitted himself to be babied at home.

*Case 7, N.M.*, white male child, 11 years of age, failed to get along with other children because he always wanted to be the boss or the chief. He made good marks in school but there, too, had no intimate classmates. He therefore spent most of his free time alone. He would then be observed to bite his nails and occasionally cry. The family physician was consulted and on examination he discovered the child's hypogenitalism. Believing the boy's misbehavior to be related to the small genitalia he referred the patient for aid in adjustment.

Examination disclosed a quiet well behaved child of 54.5 in. in height which was normal for his age. The weight was 84.5 lb., somewhat heavier than normal. The moderate obesity was distributed over the shoulder and pelvic girdles, breasts, abdomen, upper thighs and mons pubis. There was also a noticeable degree of genu valgum. The genitalia were infantile in appearance. The penis was 3 cm. in length and extremely narrow in width. The scrotum was shallow and contained a very small testis on the left side. The right testis was absent from the scrotum and could not be felt in the inguinal canal. Several days later, this testis appeared in the upper inguinal canal only to disappear again the next day. There were no neurological defects. The findings in all laboratory tests made were normal. Psychiatric survey showed no striking evidence of affective or content disorder. He did feel, however, that he ought to be the leader in games because he felt he could not let the other boys tell him what to do. At no time did he allude to his hypogenitalism, and no discussion was held at this time concerning this deficiency. Binet-Simon disclosed a mental age of 10 yr. and 10 months and the I.Q. was 98.

Treatment consisted in discussions concerning the fairness of taking turns in leadership with other children, the importance of team work for success, and a definite schedule for play with other children was prescribed. This included classes at the local gymnasium in an attempt to develop an attitude of acceptance toward the group.

Injections of testosterone propionate, 10 mg., were given three times a week for 2 weeks. At the end of this time both testes were in the scrotum and remained there. Dosage was then diminished to 5 mg., three times weekly for 2 weeks and was then further decreased to 5 mg. twice weekly for the next 8 weeks. The penis by this time was well grown, reaching a length of 6 cm. The scrotum, too, was well developed (fig. 3). As a matter of fact the whole body took on a more normal configuration. A small crine began to make its appearance. After the first month of treatment he began making a good adjustment towards his school-mates and in the gymnasium. His spirits improved. His previous attitude of belligerence toward the other boys was then brought up for discussion and it was disclosed that he had been made aware of his hypogenitalism several years earlier in a 'test' held by some older boys. From that time on he had frequently brooded over the defect but had never spoken of it to anyone.

*Case 8, D.L.*, was referred when he was 14 years and 3 months old because he had become obstinate and bashful. He had begun to gain excessive weight at 9 years of age but had apparently gotten along well with other children and at home until 1.5 years before his visit. At that time

he began associating with older boys. In contrasting his own appearance with theirs he had noticed the small size of his genitals. He then made similar comparisons with boys of his own age and observed that he 'was also smaller than they.' Evidently the other boys were making their own observations, since they began to tease him and called him 'pee wee.' Thereafter he refrained from participating in their games, remained more to himself and became bashful. The stubbornness was brought out when his mother, observing his tendency to remain at home after school, insisted upon his going out to play. Refusal on his part led to her urging him. He would then display outbursts of temper and for the rest of the day would be unwilling to do anything she asked of him. The teasing by the boys led to feelings of a lump in the throat which was present even as he spoke about it to the examiner. During the past year he had developed a twitch in the left eye which occurred mostly when he was excited or ashamed. His sleep was not disturbed but he frequently dreamed that he was a great athlete.

Physically he disclosed a normal height of 61.8 in. but a weight of 140.5 lb. which was some 30 lb. heavier than the maximum normal for that height. He showed a eunuchoid skeletal disproportion, the upper measurement being 29.0 and the lower 32.8 in. The obesity was of the shoulder and pelvic girdle type, there was a genu valgum. The penis was 1.5 cm. in length. Both testes were palpable in the scrotum but were about the size of a small almond. A sparse crines pubis had begun to appear. The results of laboratory studies were essentially normal, except that the BMR was -10. Psychiatric survey disclosed only a keen sensitivity to his abnormal configuration and hypogonadism, with mild reactions of depression, sulking, crying spells and temper tantrums. Psychometric study revealed identical mental and chronological ages.

Treatment consisted of explaining to the parents the origin of the child's bashfulness and obstinacy, the establishment in them of a more sympathetic attitude toward the child's disability and a recognition of his need for privacy during the early stages of treatment.

Discussions were held with the boy concerning the importance of maintaining social contacts, the differences existing between people generally were also stressed.

Injections of testosterone propionate, 10 mg. twice weekly, for 3 months led to a penile growth to 5 cm. (fig. 4) and a bodily configuration which took on a more normal appearance. The patient's entire attitude then changed. His personality again became characterized by the sociability which he had previously displayed.

Case 9, B.B., was 12 years and 1 month old, a boy with Frohlich bodily configuration and a penis of 1 cm. length. When at home he constantly demanded attention, insisted on being bathed by his mother and pouted at any disappointment, regardless of its triviality. He preferred to remain alone and rarely if ever joined the games of other children of his age. The mental age was 10 years and 6 months and the IQ was 87, BMR was -10.

He was treated with testosterone propionate, 25 mg. twice weekly, for one month, 10 mg. twice weekly for the next 2 months, and 5 mg. once weekly for the following month. Thyroid, 1 grain 3 times a day was also given and

dietary restriction was instituted because of the low BMR and obesity. In addition, he was encouraged to work toward a goal of greater self dependence.

By the end of 4 months the penis had become 5 cm. in length, a small crine made its appearance and there was sufficient loss in body weight to alter the entire bodily configuration. Behavior at home was described as greatly improved. He developed the ability to care for himself, began playing with boys of his own age and really took pride in his newly developed maturity.

Case 10, H.A., a white male, 13 years of age, was referred by his family physician because he was fat, had genital infantilism and was moody. By moody was meant that he periodically became quiet, sullen, irritable when spoken to, preoccupied and frequently stared into space. Physically he was of normal height, 60 in. but weighed 183 lb., at least 80 lb. overweight, and disclosed a typical Frohlich bodily configuration. The penis was so small that it could not be seen when he stood straight. The scrotum appeared bipartite, resembling labia majora. The crines was present but was of the feminine type. The left testis was felt in the scrotum and appeared to be about the size of a pea. The right testis was smaller and was situated near the external ring. The findings in neurological examination were negative. Psychiatric survey disclosed an appreciation of being different and the admission of frequently having his feelings hurt because the other boys teased him. His sullen periods were taken up with thoughts about being different from other boys. This awareness made him feel sorry for himself, and a lump would form in his throat. At these times, if the matter were discussed he would become angry. Psychometrically he disclosed a mental age of 13 years and an IQ of 115. BMR was -15, no other laboratory abnormalities were observed.

Treatment consisted of discussions in which explanations of biological variations were stressed in an attempt to create an attitude of acceptance. Encouragement was given concerning future possibilities of development. A work play program was arranged in which activities with other children would be supervised in a gymnasium. The parents were advised to refrain from discussing his moodiness with him. They were merely to report it. A restricted diet and thyroid extract 1 grain, 3 times a day were prescribed and testosterone propionate 25 mg. 3 times weekly was given by subcutaneous injection. After 2 months this dosage was decreased to 25 mg. twice weekly. One month later, 3 months after treatment had begun he still weighed 165 lb. but the genital organs had developed so well that the penis was now 6 cm. in length and both . . . . . tal development

changed. Preoccupation ceased, he became highly spirited and he had become well adjusted in the group.

Five additional patients, all presenting behavior problems of one kind or another were also found to present varying degrees of genital infantilism. These, too, responded in similar satisfactory fashion. Psychotherapy in all cases consisted of attempts to establish

acceptance at least temporarily, and afford encouragement. A brief report of these cases follows.

*Case 11, H.F.*, 15 years old, began showing signs of irritability 2 months prior to his first visit and wanted to stop school. His marks had been good but now he said he could not concentrate. The boys omitted him from their games because he was slow. Physically he showed an obesity (weight 164 lb.) but was of normal stature (60 in.) The genitals were undersized; the penis was 3 cm long and the testes were descended but small. Testosterone propionate, 25 mg twice weekly, for 3 months led to normal genital development. Dietary restriction resulted in loss of weight to 140 lb. With bodily change came improvement in emotional responses and a renewed interest in school.

*Case 12, G.E.*, 16 years and 4 months of age, displayed crying spells and loss of appetite for the past 6 months. Examination disclosed a normal height of 63 in. and weight of 110 lb. but small genitalia, although a crines was making its appearance. His friends who were now maturing were teasing him. He tried to avoid them. Psychometry disclosed a mental age of 15 years, 2 months. Testosterone propionate, 25 mg. twice weekly for 4 months resulted in a growth of genitalia so that the penis increased from its original length of 4 cm to 8 cm. At the end of 4 months he began to masturbate. Examination of the ejaculate disclosed living spermatozoa. His spirits in the meantime had undergone a remarkable improvement. The problems of masturbation and venereal disease were taken up with him and he was discharged.

*Case 13, T.Y.*, 12 years of age, had for the past year been impudent to his parents. Before this time he had been well behaved. Neither threats, punishment, nor reasoning had any effect on the boy. Examination disclosed mild obesity but normal physical measurements otherwise. The genitalia were small, the penis 2.5 cm. in length, the testes descended but pea-like in size. No basis for his misbehavior could be determined. Testosterone propionate, 25 mg. twice weekly for 2 months, followed by 10 mg doses twice weekly for 2 more months resulted in penile growth to 5 cm and testicular development to normal size. With genital development the child's behavior improved.

*Case 14, J.S.*, a 17-year-old high school student, began staying away from gym class without satisfactory reason. His parents also stated that he spoke of quitting school although he had always gotten along quite well before. Examination disclosed normally descended and fairly well developed testes but a penis 4 cm in length. In discussion he explained his recent behavior as arising from his desire to keep his knowledge to himself. A note was written to the principal asking that the temporary absence from gym class be excused. Testosterone propionate, 25 mg 3 times weekly by subcutaneous injection, resulted in a penile growth to 7 cm. in 3 months. He then returned to gym class and has been getting along very well since.

*Case 15, M.M.*, 17 years of age, began having attacks of paroxysmal tachycardia and complaints of weakness and nausea for several months. Cardiologic studies disclosed

no evidence of cardiopathy but small genitals were discovered and he was referred for treatment.

No psychogenic factors could be elicited. He was treated with testosterone propionate, 25 mg twice weekly by subcutaneous injection, and within 4 months the penis had grown from an initial 4 cm to 7 cm. From the time the penis began showing signs of growth, i.e., after the third injection, the weakness gradually improved and nausea disappeared. Since the second month of treatment there have been no tachycardial attacks.

#### DISCUSSION

The series of cases herein studied emphasizes how closely the misbehavior of this group of problem children depended upon their endocrinopathically determined somatic defects. In such patients the evidence of somatic abnormalities may be rather general as exemplified by the presence of a Frohlich bodily configuration or a eunuchoid skeletal disproportion. Frequently, however, such gross evidence of constitutional dysplasia may be entirely absent. Nor is the presence of infantile genitalia always the criterion of hypogenitalism, since in at least two of these patients the phallic development, while somewhat undersized would, under ordinary circumstances, be considered normal on routine physical examination. Such patients may well be classed as cases of masked hypogonadism.

That gonadal deficiency in laboratory animals frequently results in behavioral changes particularly involving sexual aggressiveness is quite well known (10). Such effects have been observed not only in castrated males who frequently fail to respond to the estrual female but also in spayed females who then become devoid of the cyclic receptivity, estrual courtship, peculiar vocalizations and posturings of the intact animal. The use of sex hormones experimentally has also emphasized the effect of the endocrines on such behavior. For example, testosterone propionate, the hormone used in our own studies, when administered to the newly hatched male chick or to the hen leads to premature cock-like reactions in the one (11) and to distinct masculine behavior in the other (12). When injected into castrated male guinea-pigs (13) or impotent male rats (14) the waning sex drive and capacity for copulation are again restored. That the response to this hormone is not always fixed is indicated by the female mating behavior displayed by male lizards (15) and some male albino rats (16) following such treatment.

In the human being, however, because of the increased complexity of personality structure and because of the tremendous influence of social and other experiential factors on personality development, endocrine defects, even when limited to the gonads, may influence behavior in other than mere sexual spheres. That anxiety, depression, and emotional instability



frequently accompany diminished sex drive, whether organically or psychically determined, are well known. And that these behavioral difficulties may be favorably influenced by adequate treatment with testosterone propionate has also been reported (17). In the series of cases herein studied it appears that the most frequent and probably basic cause for behavioral aberration, which in many instances not only upset the individual but also caused him to become a social problem, was an inadequate adjustment to the feeling of being different. Being different to the child usually implies being inferior. He therefore becomes inhibited, with the result that normal drives and otherwise outward expressions which ordinarily lead to the usual satisfactions of successful living, become restrained. Conflicts then arise only to be followed by circumvented types of response i.e., problem behavior. The influence of inner conflict as a genetic dynamic factor in conduct disorders has long been known (18). It is the inadequate adjustment to being different that gives rise to the difficulty and not merely the actuality of being different. In the treatment of patients with non alterable physical defects this principle becomes an important guide.

It is interesting to observe that the manner in which the child will react to his deficiency is unpredictable. It has been stated (19) that the child of the Lorraine-Levy hypopituitary type shows an 'aggressive dominant' personality while the child with the Frohlich configuration tends to be 'submissive-compliant.' On the basis of personal observation it appears that such personality relationships are not really fixed. As a matter of fact the personality reaction seems to depend largely upon the life's experiences of the individual. In the series of patients herein reported both aggressive and regressive personality types are to be found among the boys with Frohlich configuration. It does appear, however, that the patient with retarded mentality is more apt to be retiring than the one with a higher level of intelligence who more frequently becomes overly-aggressive. But each case must be approached individually and psychotherapy must be utilized in accordance with the patient's needs. For the most part this consists of re-education, the use of a well planned routine best adapted to the needs of the patient, and the correction of irritating influences in the home situation.

The use of specific hormone therapy is extremely important since only in this way is it possible to alter those original somatic defects which initiated the difficulty. The use of testosterone propionate in these cases, because it so rapidly developed the genitals to a more normal size, may, therefore, be considered to have had a profound therapeutic effect. The dosage of this hormone, like that of other endocrine preparations, must be graded in accordance with the degree

of structural deficiency. In well-marked hypogonadism a dosage of 25 mg., 3 times weekly appears to be satisfactory. This dosage can then be decreased both in amount and frequency as improvement occurs. It is interesting to note that in a number of patients this hormone not only led to phallic growth but in several instances also resulted in the descent of previously undescended testes and even to testicular growth.

This latter observation is particularly noteworthy since testosterone propionate has been described as causing structural testicular defects in the rat (20, 21) and depression of testicular function as judged by decreased sperm output in the human being (22, 23). From personal experience, both experimentally and clinically (24, 25), it may be said that if testosterone propionate is observed to produce deleterious effects on the testis, it probably indicates that too much of the hormone has been used in that particular individual. This opinion is based not only on the experimental observation that suitably small, although still androgenically potent, dosages failed to depress the testis (26) but also on the fact that the testis of the normal adolescent boy continues to grow in spite of the secretion of progressively higher concentrations of androgens (27).

Finally, it is important to emphasize the complexity of the problem which embraces the endocrinopathic child who misbehaves. Fortunately, the patients reported in this communication responded well. Others, less fortunate however, failed to alter their behavioral tendencies in spite of improvement in their physical defects (28). In these it appears that a basic psychopathic propensity was so deep rooted constitutionally that they lacked that plasticity which must be present if there is to be benefit from psychotherapy.

#### SUMMARY

Children with defective personality reactions frequently display endocrinopathic somatic defects. In a group of 15 such boys the behavior difficulties were found to be directly related to the frank or masked hypogonadism. Treatment with testosterone propionate, usually commencing with 25 mg., 2 or 3 times weekly, led to phallic growth in all cases. In several patients with undescended testes, testicular descent and growth also resulted. Concomitant psychotherapy was also used. This consisted of discussions with a view toward re-education, the establishment of a planned routine to include supervised activities in a group, and the restoration of more healthy home situations.

All of the patients responded by establishing more satisfactory attitudes toward their defects and all developed a more acceptable behavior. The complexity of the problem is emphasized, however, by calling attention to other dysplastically constituted behavior.



ior-problem children who failed to improve in their behavior even after the physical defects had been corrected.

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# Pubertas Precox in A Six-Year-Old Boy Produced by a Tumor of the Testis, Probably of Interstitial Cell Origin

## [[Neoplastic Hypergenitalism]]

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GNADAL HYPERFUNCTION may be divided into two general types, a), primary and b), secondary. There has been some doubt that such an entity as primary hypergonadism exists, provided the gonads are situated normally, especially with our newer knowledge of the essentiality of the anterior pituitary gonadotropic hormone or hormones for gonadal development and function. However, this conception does not take into consideration the possibility of tumors, interstitial cell or adrenocortical, the secretions of which may have androgenic activity.

Pubertas precox may be due to four known factors, a), anterior pituitary hyperfunction, b), pineal disturbance, c), certain adrenal cortex tumors or disturbances and d), interstitial cell tumor of the testis.

There are frequent instances of precocious puberty produced by anterior pituitary gonadotropic hormones, especially in girls, as evidenced by secondary sexual development, early epiphyseal closure and onset of menstruation. Werner (1) cited two cases in which menstruation began at 1 and 7 years, respectively, with no other evident glandular imbalance and with normal hypophyseal fossae.

There has been some controversy (1) as to whether hypofunction or hyperfunction of the pineal gland may cause precocious puberty. Precocious puberty has been found accompanying certain teratomas of the pineal gland (2). It would seem logical that if the pineal is capable of influencing secondary sexual development abnormally, it would be due to hyperfunction.

Between the seminiferous tubules of the testes, in the loose connective tissue supporting them, there are clumps of cells known as interstitial cells or cells of

Leydig, also spoken of as the interstitial glands. These interstitial cells are the source of the internal secretion, testosterone, which is responsible for the development of the male secondary sex characteristics and sexual instinct. Normally, these cells do not function sufficiently to cause secondary sexual development until the time of puberty when they are stimulated to activity by the anterior pituitary gonadotropic hormone. Interstitial cells are much more sparse in the testes of children than in adults. Stewart (3) states 'In old individuals, especially if the seminiferous tubules are atrophic, the interstitial cells may be notably increased. An increase in their number has frequently been observed in atrophic testes, especially in undescended testes; the seminiferous tubules are atrophic and the interstitial cells are prominent. Apparently the interstitial cells may increase when for any reason the seminiferous tubules fail to develop or become atrophic; but such hyperplasia does not occur in cases of orchitis with destruction of the tubules from inflammatory overgrowth of the intertubular connective tissue.'

Interstitial cell tumors cause less apparent disturbance in adults than in children because the secondary sexual characteristics are developed, but the tumors have the same histological picture.

Interstitial cell tumors in adults have been described by Kaufman (4), Stoppato (5), and Villata (6).

Sacchi (7) reported pubertas precox in a boy 9 years of age who had an alveolar carcinoma of the left testis. Stewart, Bell and Roehlke (3) reported the case of a 5-year-old child who had an interstitial-cell tumor of the right testis with the sexual phenomena characteristic for puberty.

Rowlands and Nicholson (8) published the report of a boy who, at the age of 6 years, began to show

progressive evidences of precocious sexual development. At the age of 9 years the left testis, which was enlarged, was removed and an interstitial cell tumor was proved microscopically.

#### CASE REPORT

Our patient, when first observed, was 6 years and 9 months of age. He was a first child, born at full term and the delivery was normal. His weight at birth was 8.75



Fig. 1. Patient, aged 6 years and 9 months. Note marked secondary sexual, skeletal and somatic development.

pounds. The first teeth erupted at 6 months; he talked and walked at one year and was continent at 15 months, all of which are within normal developmental limits. He is in the second grade at school, learns well, makes good grades and his social contact has been normal until recently.

About 15 months ago, when he was 5.5 years of age, his mother first noticed abnormal hair growth about the external genitals, which were larger than normal at that time. The external genitals continued to increase in size (fig. 1) and he had frequent erections. The hair growth about the genitals became more marked and hair began to grow in the axillae, on the lips, chin and face. He was taller than normal for his age, the bodily configuration was heavier and the muscles in general were prominent and firm. The facial features became of the late adolescent type and during the past month the voice had become deeper in tone and had more volume.

About two months before observation by one of us (A. A. W.) he was found in a garage caressing a 6-year-old girl. This alarmed his mother and caused her to seek advice.

An interesting bit of information was obtained from the mother. Since he was two years of age he has smoked as many as 50 cigars without becoming ill. These were given to him by people other than his mother who, when she knew of it, would forbid his smoking.

*Personal history.* He sleeps soundly, his appetite is very good and he drinks no coffee or tea. He has had measles and mumps; no operations. The father and mother are living and well and he is the only child.

*Physical examination.* His height is 53.75 inches; the normal height for his age is 45 to 48 inches; his weight is 73.75 pounds, the normal being 42 to 52 pounds. The upper measurement is 26.25, the lower 27.5 inches and one-half span is 26.25 inches. The hands are very broad and the fingers are relatively short. The body is warm and the skin has normal moisture. The boy is large and has general skeletal development characteristic for a boy from 10 to 12 years of age. The muscles are overdeveloped for his age and are firm. The hair of the scalp is heavy and coarse. There is increased hair growth on the upper lip.

The penis, when flaccid, is 3.75 inches long and 1.5 inches in diameter, with glans in proportion. The left testicle is about 8 mm. in diameter and 1 cm. long. The right testicle is the size of a medium-sized olive. Both testicles show increased firmness. There is marked hair growth over the scrotum and pubis. The inguinal and femoral lymphatic glands are palpable, moderately enlarged and firm. The prostate is palpable, shows moderate development and the consistency is soft. All of the deciduous teeth are present, except the two lower central incisors which are permanent teeth; they are only partially erupted. The thyroid is about normal in size. Examination of the lungs and heart is negative; the pulse is 80, the blood pressure is 110 mm. Hg systolic and 70 diastolic. There is no abdominal dullness over the back, in the lower thoracic or upper lumbar regions or in the abdomen which might be suggestive of adrenal tumor. The kidneys are not palpable.

*Laboratory findings.* Blood studies showed Hb., 84 per cent; red cells, 4,200,000; white cells, 7150; differential count, juvenile 3, stabs 10, segmented 68, lymphocytes, 20; monocytes, 1 to 2; blood group, 4; results of the Kahn test, negative; non-protein nitrogen, 27 mg. per cent; blood sugar, 100 mg. per cent; chlorides, 512 mg. per cent; diastase 98 units (normal range 80 to 150); calcium 11.1 mg. per cent; total protein, 7.4 gm. per cent; albumin, 4.8 gm. per cent; globulin, 2.6 gm. per cent; serum inorganic phosphorus 9.6 mg. per cent (normal for children, 4-6); phosphates, 5.2 Bodansky units (normal 5 to 12 units); cholesterol, 162 mg. per cent. Results of sugar tolerance test in mg. per cent: fasting, 72; one hour, 125; 2 hours, 108; 3 hours, 80; 4 hours, 72.

The Friedman test of the urine for gonadotropins was negative. Basal metabolic rate was -14 and -15 per cent.

Roentgenograms show markedly advanced bone development. There are no abnormal shadows over the renal

or adrenal regions and the kidney pelvis shadows are normal

It was suspected that there was a tumor of the right testis (Vitt) This gonad was removed Feb 13, 1942

**Pathologist's report** The specimen consisted of a testis measuring 2.5 by 1.5 cm. Near one pole could be felt a nodule of firmer consistency than the surrounding tissue. Section through the long axis of the testis showed this firm area to be a yellowish gray tumor, of roughly oval shape and measuring 12 mm. in maximum diameter (fig. 2). The small tumor was situated just beneath the capsule of the testis, and protruded inward in such a fashion as to displace a considerable portion of the testicular tissue. The tumor nodule was quite circumscribed and appeared sharply separable from the testicular tissue.

Microscopically, the tumor consisted of rather dense masses and columns of cells separated by a thin, scanty connective tissue stroma. In some areas thin elongated columns of cells formed the predominant arrangement, and produced an appearance suggestive of the columns of the adrenal cortex. In other areas there were small rounded, oval, or irregular groups of cells separated by the thin stroma. The individual cells were of oval or polyhedral shape, usually with prominent cell boundaries and abundant faintly eosinophilic granular cytoplasm. The nuclei were oval, slightly eccentric, and often contained a single prominent nucleolus. The cells were all similar, showing but little variation in size, shape or staining properties. Some cells were large due to abundant cytoplasm, but the nuclei showed no variation, and mitoses were not seen. Staining by Sudan III and osmic acid revealed no stainable lipid content of the tumor cells. Near the periphery of the tumor a few atrophic testicular tubules were

surrounded by tumor cells but, for the most part, the tumor was sharply separated from adjacent testicular tissue by a thin connective tissue band (fig. 3 and 4).

The tumor tissue in its microscopic appearance was rather strongly reminiscent of the adrenal cortex because of the columnar arrangement, which was prominent in some areas, and because of the abundant, slightly granular cytoplasm of the individual cells. However, the cells had a morphology similar to the interstitial cells of the testis. The interpretation of the nature and origin of the



Fig. 2 Tumor of the testis removed from patient aged 6 years and 9 months

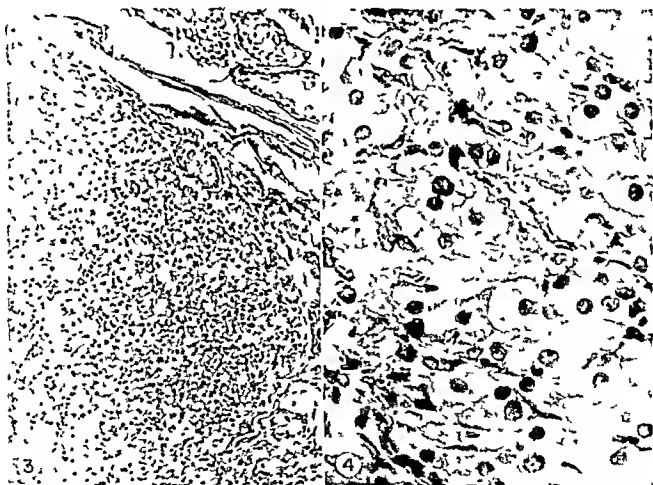


Fig. 3 Low power photomicrograph of the tumor of testis. Fig. 4 High power photomicrograph of the tumor showing cells resembling interstitial cells.

tumor cells would seem to be that they were either adrenal cortical tissue or interstitial cells of the testis. The histological appearance was similar to that of the interstitial cell tumor of the testis reported by Stewart, Bell and Roelke (3). Through the courtesy of Dr. M. K. Shimken, sections of the tumor were compared with those of interstitial cell tumors of the testis induced in mice by injec-

tion of stilbestrol. They were found to be closely similar. The weight of evidence suggests that the probable diagnosis is interstitial cell tumor of the testis.

On June 1, 1942, (3.5 months after operation) an examination of the boy showed the facial expression to be more child-like, the coarse hair on the upper lip has disappeared, there is less genital hair growth, the penis is about the same length but the glans seems smaller. The left testicle has increased in size to that of a medium-sized olive and has normal consistency. The voice has not returned to normal pitch. His mother states that 'his aggressive attitude has changed to gentleness and he wants to be around his mother. Formerly he wanted to be with adults and did not want to play with children of his own age; now he shuns adults and seeks the companionship of children.'

In the past 8 months he has grown 1.75 inches and his weight has increased 5 pounds.

#### SUMMARY

Hypergenitalism was first noticed in a boy at 5.5 years of age, when the mother found abnormal hair growth about the external genitals, which were larger than normal at that time. At 6 years, 9 months, of age the external genitals were adult in size, there was marked genital and pubic hair growth, with moderate hair growth on the upper lip, chin, face and in the axillae. The voice was deep in tone, and of considerable volume; the facial features were adolescent in type. He was at least 6 inches taller and 20 pounds heavier than normal for his age. The muscles were overdeveloped and firm. He sought the company of adults, and libido had been manifested. Roentgenograms showed markedly advanced bone development.

The right testis, including the tumor, was surgically removed. The pathological interpretation is that the tumor was either a), derived from an adrenal rest in the testis, or b), that it was an interstitial cell tumor, the weight of evidence being strongly in favor of the latter.

Three and one-half months after the operation there was evidence of regression of the abnormally developed secondary sexual characteristics.

#### CONCLUSIONS

1. A study of this patient suggests strongly that the secretion of the interstitial cells of the testis may cause development of secondary sexual characteristics in the male.

2. This study also presents further evidence that the secretion of the interstitial cells may accelerate skeletal and somatic growth and development.

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# Comparative Values of Chorionic Gonadotropic Hormone and Testosterone Propionate in Treatment of Cryptorchidism and Hypogonitalism

## [Treatment of Cryptorchidism]

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THE PRESENT COMMUNICATION is based upon the results obtained by the administration of chorionic gonadotropic hormone alone or in alternation with male sex hormone in twenty-five boys and one adult with cryptorchidism and hypogonitalism. The cases are subdivided as a), those of cryptorchidism in which chorionic gonadotropic hormone alone was administered, b), those with cryptorchidism in which male sex hormone was administered in alternation with chorionic gonadotropic hormone, either after the unsuccessful use of the latter or without previous treatment and c), cases of hypogonitalism treated with one or both of the hormones.

All of the patients were studied in accordance with the methods and procedures described in previous communications. These include a complete physical examination, roentgenographic studies of the sella turcica and of the wrists, basal metabolic tests, specific dynamic action and blood chemistry studies (1). The effect on the cryptorchidism and on the external genitalia will be discussed in the present report, while that on the height, growth and bone development is considered in a separate communication. All cases of cryptorchidism in this series are of the true type. Testes of the receding type or those which could be forced into the scrotum by either manipulation or heat are considered as instances of pseudo cryptorchidism and are not included.

Group 1 This group consists of 18 boys with cryptorchidism, ranging in age from 5 5/8 to 14 5/8 years. The condition occurred in boys who were otherwise normal in 7 instances, in 10 boys with adiposogenital dystrophy and in one with adiposogenital dystrophy and eunuchoidism. There were 10 cases of unilateral involvement and 8 of bilateral, the un-

descended testis was in the abdomen in 4 of the bilateral and in 5 of the unilateral cases and in the inguinal canal in the same distribution. The condition of the external genitalia was as follows: Normal, 2 cases, both with unilateral cryptorchidism; underdeveloped, 14 cases (8 with bilateral and 6 with unilateral cryptorchidism), and overdeveloped, two cases, both with unilateral cryptorchidism.

The treatment in this group consisted of the intramuscular injection of chorionic gonadotropic hormone<sup>1</sup> in doses of from 250 to 500 R.U. twice a week. This was changed to an equivalent number of IU after the introduction of the latter standard. The dosage ranged from a minimum of 3000 to a maximum of 20,000 IU, with an average of 8650 IU in the successful cases (those with complete descent of the testes), and a range of 15,800 to 64,000 IU in the average of 39,480 IU in the unsuccessful cases. The duration of treatment varied from 2 to 9 5/8 months, with an average of 4 5/8 in the successful cases; from 5 to 22 months in the unsuccessful with an average of 12 5/8 months. Treatment was continuous for about 3 months, discontinued for one or two months and then resumed, if necessary. Supplementary treatment was given as indicated, boys with adiposogenital dystrophy received an appropriate diet high in proteins and low in carbohydrates and fats, with adequate supply of vitamins and oral administration of desiccated thyroid and anterior pituitary substances.

In evaluating the results, a testis was considered to be completely descended when it entered into the scrotum and remained there. Descent as far as the external ring or to the upper border of the scrotum

<sup>1</sup> The chorionic gonadotropic hormones were supplied as a), Pregnyl, Roche Organon, Inc., Nutley, N. J., b) Follutein, E. R. Squibb and Son, New Brunswick, N. J., and c), A. P. L. Ayerst, McKenna and Harrison, Rouses Point, N. Y.

was listed as partial descent. In a few instances the testis descended into the scrotum and then retracted, but eventually remained in the scrotum after further treatment. In these cases, the latter date was considered as that of complete descent.

Treatment of cryptorchidism by chorionic gonadotropic hormone in this group resulted in complete descent in 45 per cent, partial descent in 33 and none in 22 per cent. The response was better in the in-

TABLE 1. EFFECTS OF CHORIONIC GONADOTROPIC HORMONE ON CRYPTORCHIDISM

| Types of Cryptorchidism                   | Total Number | Complete Descent |      | Partial Descent |      | No Descent |      |
|---|--------------|------------------|------|-----------------|------|------------|------|
|   |              | No               | %    | No.             | %    | No.        | %    |
| Unilateral                                | 10           | 3                | 30   | 5               | 50   | 2          | 20   |
| Bilateral                                 | 8            | 5                | 62.5 | 1               | 12.5 | 2          | 25   |
| Abdominal                                 | 9            | 3                | 33.3 | 3               | 33.3 | 3          | 33.3 |
| Inguinal                                  | 9            | 5                | 56   | 3               | 33   | 1          | 11   |
| Total                                     | 18           | 8                | 45   | 6               | 33   | 4          | 22   |
| Associated conditions                     |              |                  |      |                 |      |            |      |
| A. Normal boys                            |              |                  |      |                 |      |            |      |
| unilateral                                | 5            | 0                | 0    | 3               | 60   | 2          | 40   |
| bilateral                                 | 2            | 1                | 50   | 1               | 50   | 0          | 0    |
|   | 7            | 1                | 14   | 4               | 57   | 2          | 29   |
| B. Boys with adiposogenital dystrophy and |              |                  |      |                 |      |            |      |
| unilateral                                | 4            | 3                | 75   | 1               | 25   | 0          | 0    |
| bilateral                                 | 6            | 4                | 66.6 | 0               | 0    | 2          | 33.3 |
| eunuchoidism and unilateral               | 1            | 0                | 0    | 1               | 100  | 0          | 0    |
|   | 11           | 7                | 64   | 2               | 18   | 2          | 18   |

guinal type of cryptorchidism. Irrespective of location, better results were obtained in bilateral than in unilateral involvement, as gauged by the incidence of complete descent. Partial descent, however, resulted more frequently in the unilateral type.

Total failure was observed in two cases of unilateral cryptorchidism in normal boys with a definite history of mechanical obstruction due to previous operations, and in two instances of bilateral cryptorchidism with adiposogenital dystrophy.

This is too small a series upon which to base definite conclusions, but a comparison between the results in the apparently normal boys and in those with adiposogenital dystrophy supports our contention that supplementary treatment is necessary and is beneficial in the endocrine type of cryptorchidism. Complete descent was obtained in the boys with adiposogenital dystrophy in 64 per cent, partial descent in 18 per cent and a failure of descent in 18 per cent of the cases. Complete descent occurred in 14 per cent, partial in 57 per cent and none in 29 per

cent in the normal boys. If we exclude the two cases of failure due to mechanical causes, in which medical treatment could never be of benefit, the percentage of complete descent in the normal group is still lower (40 per cent) than in the endocrine group.

The best response to treatment with chorionic gonadotropic hormone was obtained in the 9 to 11-year age group, excluding the isolated case of a 5.5-year-old boy.

*Group 2.* This group consists of 6 patients with cryptorchidism, 5 from 9 to 15 years of age and one adult of 30 years. The boys had had previous treatment with various preparations of chorionic gonadotropic hormone; 3 of them had been treated intensively by us. There were 3 instances of bilateral abdominal cryptorchidism and 3 with unilateral inguinal involvement. Three of the boys had had an initial adiposogenital dystrophy which had improved under treatment, 2 were normal boys and the adult presented the obese type of eunuchoidism with unilateral cryptorchidism.

Testosterone propionate<sup>2</sup> was administered twice a week in strengths of 5 to 10 mg. and further dosage was adjusted to the individual requirements and response. An increase to 25 mg. twice a week was considered necessary in 3 of the older boys. The adult received 25 mg. 3 times a week from the beginning of treatment. Testosterone propionate was continued for 4 to 8 weeks and then discontinued and chorionic gonadotropic hormone administered from 1 to 3 months. This alternation was adhered to for the entire period of treatment except for intervals lasting from several weeks to several months.

The dose of the chorionic gonadotropin averaged 12,425 R.U. The duration of treatment varied from 2 to 9 months with an average of 5.5. The adult received a total of 1750 mg. of testosterone propionate, as a result of which partial descent occurred; 5000 I.U. of chorionic gonadotropic hormone produced complete descent. None of the boys showed any response in the descent of the cryptorchid. A partial response was observed in the adult after 3 months of administration of testosterone propionate, as evidenced by a descent of an abdominal cryptorchid into the lower third of the inguinal canal and into the upper part of the scrotum, but with retraction. Administration of 1000 I.U. of chorionic gonadotropic hormone twice a week was followed by ultimate descent into the scrotum.

*Group 3.* There were 20 patients with underdeveloped genitalia. Three of these were boys who presented a clinical picture of adiposogenital dystrophy and eunuchoidism. One was a boy of 10 years and 11

<sup>2</sup> The testosterone propionate was supplied by Roche-Organon, Inc., Nutley, N. J., as Neo-Hombreol, and as Oreton by Schering Corp., Bloomfield, N. J.

months with primary eunuchoidism and gigantism, one was an adult, 30 years of age, who showed the obese type of eunuchoidism and unilateral cryptorchidism, 15 were boys with various grades of hypogonadism. The penis ranged in size from that of infantile to somewhat less than normal for the age. The scrotum varied from a flaccid scrotum with no pouch to one of fairly normal size and appearance. The testes were descended in 5 cases and undescended in 15, in the former cases practically all of the testes were smaller than normal but none was atrophied. The three components of the external genitalia, penis, scrotum and testes, showed the same tendency to underdevelopment, but in a number of instances the scrotum was normal and the testes hypoplastic, and vice versa.

Chorionic gonadotropic hormone was administered to 19 boys and in alternation with testosterone propionate to 10 patients. In the cases with associated cryptorchidism, treatment was continued after descent of the testes had been obtained in order to further stimulate the testicular function.

The effects of treatment upon hypogonadism and hypogonadism were evidenced by increase in the size of the external genitalia, appearance of secondary sex characteristics and by psychological changes. The younger boys showed a favorable response in the size of the penis, scrotum and descended testes and at times by the premature appearance of pubic hair and turgescence of the scrotum. In the older boys there ensued the development of pubic, axillary, and, later, of facial hair, deepening of the voice, enlargement of the penis, testes and scrotum, turgescence of the scrotum, occasional priapism and nocturnal emissions. The effects on the size of the penis, scrotum and testes were not always parallel, that is, for example, growth of the penis was not always

change in his psychological attitude. In the boys with adiposogenital dystrophy there was a marked change in body contour with a reversion to the male type of build with a loss of adiposity in general, especially in the mammary, abdominal and trochanteric regions.

The successive treatment with testosterone propionate and chorionic gonadotropic hormone was more effective in correcting genital hypoplasia and developing secondary sex characteristics than chorionic gonadotropic hormone alone. Of those patients

TABLE 3. EFFECT OF TREATMENT OF CRYPTORCHIDISM AT DIFFERENT AGES

| Age Group, Years | Total Number | Complete Descent |     | Partial Descent |    | No Descent |    |
|------------------|--------------|------------------|-----|-----------------|----|------------|----|
|                  |              | No               | %   | No              | %  | No         | %  |
| 5-5              | 1            | 1                | 100 |                 |    |            |    |
| 8 to 9           | 5            | 1                | 20  | 2               | 40 | 2          | 40 |
| 9 to 11          | 7            | 4                | 57  | 3               | 43 | 0          | 0  |
| 11 to 14 5       | 5            | 2                | 40  | 1               | 20 | 2          | 20 |

treated with the latter, the penis attained normal proportions and appearance in 8 cases, it became slightly overdeveloped in 2 and remained underdeveloped in 9. The use of combined treatment in the latter 9 patients was followed by an increase in size and development of the penis in 3 cases, the development of normal proportions in 5 and persistent underdevelopment in one. The testes in all of the successful cases were normal or slightly enlarged and never atrophied.

The average dosage of the chorionic gonadotropin for the group was 21,788 R.U. over a period of 9.5 months; that of testosterone propionate was 320 mg. over 4.5 months.

#### DISCUSSION

Cryptorchidism is being treated currently either by endocrine therapy or by surgical procedure or by combination of both. The endocrine agents which are being used are chorionic gonadotropic hormone from pregnancy urine, chorionic gonadotropic hormone from pregnant mare serum, gonadotropic hormone from the anterior pituitary lobe and synthetic male sex hormone, testosterone propionate.

Our studies confirm those of others that chorionic gonadotropic hormone from pregnancy urine is the most efficient type of therapy, but the degree of efficiency is still a debatable subject. Successful outcome, that is, complete descent of the testes into the scrotum, is obtained, on the average, in from 30 to 50 per cent of the cases, ranging from enthusiastic reports of 73 per cent (2-5) to pessimistic results of 20 per cent (6). Our present results of 45 per cent success is midway between these figures. None of the usual arguments against the higher figures is applicable in our study, as we meticulously excluded all in-

TABLE 2. EFFECTS OF ALTERNATING ADMINISTRATION OF CHORIONIC GONADOTROPIC HORMONE ON CRYPTORCHIDISM

| Age Group | Total Number | Complete Descent | Partial Descent | No Descent |
|-----------|--------------|------------------|-----------------|------------|
| Boys      | 5            | 0                | 0               | 5          |
| Adult     | 1            | 1                | 0               | 0          |

accompanied by enlargement of the scrotum and testes. In practically every one of the older boys with bilateral cryptorchidism in whom treatment was unsuccessful, there was enlargement of the phallus and scrotum, and the appearance of pubic hair, in spite of nondescent of the testes. Acne appeared in a few boys. A more aggressive attitude in general, and an awakening interest in girls were noted in some of the older boys. The eunuchoid adult in addition to the changes described above, experienced libido and a



was listed as partial descent. In a few instances the testis descended into the scrotum and then retracted, but eventually remained in the scrotum after further treatment. In these cases, the latter date was considered as that of complete descent.

Treatment of cryptorchidism by chorionic gonadotropic hormone in this group resulted in complete descent in 45 per cent, partial descent in 33 and none in 22 per cent. The response was better in the in-

cent in the normal boys. If we exclude the two cases of failure due to mechanical causes, in which medical treatment could never be of benefit, the percentage of complete descent in the normal group is still lower (40 per cent) than in the endocrine group.

The best response to treatment with chorionic gonadotropic hormone was obtained in the 9 to 11-year age group, excluding the isolated case of a 5.5-year-old boy.

**Group 2.** This group consists of 6 patients with cryptorchidism, 5 from 9 to 15 years of age and one adult of 30 years. The boys had had previous treatment with various preparations of chorionic gonadotropic hormone; 3 of them had been treated intensively by us. There were 3 instances of bilateral abdominal cryptorchidism and 3 with unilateral inguinal involvement. Three of the boys had had an initial adiposogenital dystrophy which had improved under treatment, 2 were normal boys and the adult presented the obese type of eunuchoidism with unilateral cryptorchidism.

Testosterone propionate<sup>2</sup> was administered twice a week in strengths of 5 to 10 mg. and further dosage was adjusted to the individual requirements and response. An increase to 25 mg. twice a week was considered necessary in 3 of the older boys. The adult received 25 mg. 3 times a week from the beginning of treatment. Testosterone propionate was continued for 4 to 8 weeks and then discontinued and chorionic gonadotropic hormone administered from 1 to 3 months. This alternation was adhered to for the entire period of treatment except for intervals lasting from several weeks to several months.

The dose of the chorionic gonadotropin averaged 12,425 R.U. The duration of treatment varied from 2 to 9 months with an average of 5.5. The adult received a total of 1750 mg. of testosterone propionate, as a result of which partial descent occurred; 5000 I.U. of chorionic gonadotropic hormone produced complete descent. None of the boys showed any response in the descent of the cryptorchid. A partial response was observed in the adult after 3 months of administration of testosterone propionate, as evidenced by a descent of an abdominal cryptorchid into the lower third of the inguinal canal and into the upper part of the scrotum, but with retraction. Administration of 1000 I.U. of chorionic gonadotropic hormone twice a week was followed by ultimate descent into the scrotum.

**Group 3.** There were 20 patients with underdeveloped genitalia. Three of these were boys who presented a clinical picture of adiposogenital dystrophy and eunuchoidism. One was a boy of 10 years and 11

TABLE 1. EFFECTS OF CHORIONIC GONADOTROPIC HORMONE ON CRYPTORCHIDISM

| Types of Cryptorchidism                   | Total Number | Complete Descent |      | Partial Descent |      | No Descent |      |
|---|--------------|------------------|------|-----------------|------|------------|------|
|   |              | No.              | %    | No.             | %    | No.        | %    |
| Unilateral                                | 10           | 3                | 30   | 5               | 50   | 2          | 20   |
| Bilateral                                 | 8            | 5                | 62.5 | 1               | 12.5 | 2          | 25   |
| Abdominal                                 | 9            | 3                | 33.3 | 3               | 33.3 | 3          | 33.3 |
| Inguinal                                  | 9            | 5                | 56   | 3               | 33   | 1          | 11   |
| Total                                     | 18           | 8                | 45   | 6               | 33   | 4          | 22   |
| Associated conditions                     |              |                  |      |                 |      |            |      |
| A. Normal boys                            |              |                  |      |                 |      |            |      |
| unilateral                                | 5            | 0                | 0    | 3               | 60   | 2          | 40   |
| bilateral                                 | 2            | 1                | 50   | 1               | 50   | 0          | 0    |
|   | 7            | 1                | 14   | 4               | 57   | 2          | 29   |
| B. Boys with adiposogenital dystrophy and |              |                  |      |                 |      |            |      |
| unilateral                                | 4            | 3                | 75   | 1               | 25   | 0          | 0    |
| bilateral                                 | 6            | 4                | 66.6 | 0               | 0    | 2          | 33.3 |
| eunuchoidism and unilateral               | 1            | 0                | 0    | 1               | 100  | 0          | 0    |
|   | 11           | 7                | 64   | 2               | 18   | 2          | 18   |

guinal type of cryptorchidism. Irrespective of location, better results were obtained in bilateral than in unilateral involvement, as gauged by the incidence of complete descent. Partial descent, however, resulted more frequently in the unilateral type.

Total failure was observed in two cases of unilateral cryptorchidism in normal boys with a definite history of mechanical obstruction due to previous operations, and in two instances of bilateral cryptorchidism with adiposogenital dystrophy.

This is too small a series upon which to base definite conclusions, but a comparison between the results in the apparently normal boys and in those with adiposogenital dystrophy supports our contention that supplementary treatment is necessary and is beneficial in the endocrine type of cryptorchidism. Complete descent was obtained in the boys with adiposogenital dystrophy in 64 per cent, partial descent in 18 per cent and a failure of descent in 18 per cent of the cases. Complete descent occurred in 14 per cent, partial in 57 per cent and none in 29 per

<sup>2</sup> The testosterone propionate was supplied by Roche-Organon, Inc., Nutley, N. J., as Neo-Hombreol, and as Oreton by Schering Corp., Bloomfield, N. J.

gonadotropic hormone. The former should not be administered to boys under 9 or 10 years of age. Prolonged treatment should not be advised except in cases of primary eunuchoidism, but small maintenance doses may be given for comparatively short intervals in milder grades of hypogonadism, perhaps in cryptorchidism and in selected cases of short stature. An average dose of 10 mg twice a week for 1 to 3 months is sufficient to produce the desired therapeutic response without any untoward effects in most instances of hypogonadism. These effects, consisting of excessive growth of the penis, premature appearance of secondary sex characteristics, priapism, emissions and stimulated sex interest, may be produced in a small number of cases but they can be controlled by adjustment of the dose to the individual needs of the patient. Some authors report premature closure of the epiphyses and impairment of growth but we have not observed either of these in our present series.

Treatment for cryptorchidism with chorionic gonadotropin should be instituted between the ages of 5 to 9 years and should not be delayed until after puberty in the hope of spontaneous descent.

#### SUMMARY AND CONCLUSIONS

Chorionic gonadotropic hormone was administered to 18 boys with true cryptorchidism with the following results: Complete descent occurred in 45 per cent, partial descent, 33 per cent and no descent in 22 per cent. Better response was obtained in the cases of bilateral and in the inguinal types of cryptorchidism.

Boys with adiposogenital dystrophy were given supplementary treatment of desiccated thyroid and anterior pituitary substances and a diet high in protein and low in fats and carbohydrates. Better results were obtained in this type of boy than in the apparently normal boy.

Testosterone propionate was administered subsequent to and in alternation with therapy with chori-

onic gonadotropic hormone to 5 boys with cryptorchidism and to one adult with unilateral cryptorchidism associated with the obese type of eunuchoidism. Three of these boys had had previous treatment with chorionic hormone without success. The alternating administration of both hormones did not produce any further descent of the testes in the boys. Testosterone propionate produced a partial descent of an abdominal cryptorchid in the eunuchoid adult and subsequent administration of chorionic gonadotropic hormone was followed by complete descent.

Chorionic gonadotropic hormone was given to 19 boys with hypogonadism, in alternation with testosterone propionate to 9 boys in whom the first type of treatment was unsuccessful, and to one eunuchoid adult who had not received previous treatment.

We conclude that the administration of chorionic gonadotropic hormone is more effective in producing complete descent of undescended testes than is testosterone propionate alone, or in alternation with chorionic gonadotropin. Supplementary treatment is necessary and beneficial in the cryptorchid boy with an associated adiposogenital dystrophy or hypothyroidism.

Testosterone propionate alone or in alternation with chorionic gonadotropic hormone is more effective than the latter in the treatment of hypogonadism.

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## ENDOCRINOLOGY AND PSYCHOSOMATIC MEDICINE

THERE IS NOW apparent in the field of clinical medicine a strong trend toward the recognition of the part played by psychological factors in the causation of physical symptoms. Equally important is the relationship of physical factors in the genesis of 'psychological' disorders. So intimately related are the two categories of causes and of effects that their separation amounts, in principle, to a falsification of the issue—a recourse to dogmatic artificiality. In modern psychological and psychiatric circles the differentiation of psyche and soma has come to be recognized as a gratuitous over-simplification that cannot do justice to the essential facts. A sick man is a sick man whether his illness arises primarily in structural defects or in his life experiences. It is less than scientific to confine attention to either the somatic or the psychological facet of the total individual. The physician is doing less than his full duty to the patient when he fails to give his attention to the real etiology, whatever it may be, and to utilize appropriate therapeutic agencies of any legitimate sort whether drugs, hormones, physical therapy, re-educat-

tion, or what not. Often a skilful combination of two or more therapeutic modalities leads to results better than can be obtained by any single method of treatment.

Endocrinologists, as a group, have tended to be somewhat reluctant to follow the leadership of sophisticated internists toward the goals of psychosomatic medicine. But perhaps the time has now come to give more attention to the man that has the glands rather than merely to the glands themselves and to the bodily effects of their perturbations.

Elsewhere in this issue appears an article by Rubenstein in which the eclectic approach is exemplified. A group of boys suffering from retarded genital development were studied with regard to the psychotraumatic results of their infirmity. Not only was androgen therapy prescribed but attempts were made to remove the scars of the personality by appropriate re-educational psychotherapy.

The field of endocrinology offers many opportunities for further studies of psychodynamics. In such studies the technical resources of trained psychologists are often needed for penetrating approaches to the problems but at this juncture even the elementary aspects of the subject offer possibilities for productive instigation.

R.G.H.



# COMMUNICATIONS TO THE EDITORS

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## TO THE EDITOR

Sir: It has come to my attention that there is now considerable confusion regarding the strength of "Hytakerol" which is the only source of Dihydrotachysterol available in this country. The matter is a rather important one since all the work on this product in this country, including several papers of my own, have been carried out on the assumption that there were 5 mg per 1 cc instead of 1.25 mg, as seems to be the case.

FULLER ALBRIGHT

*This letter was submitted to the Winthrop Chemical Company and the following was received:*

## TO THE EDITOR

Thank you for calling to our attention the enclosed letter from Dr. Fuller Albright regarding an apparent discrepancy in labels of Hytakerol (our brand of dihydrotachysterol) of old and recent manufacture. Formerly the labels of Hytakerol in Oil bore the statement that 1 cc contains 5 mg of dihydrotachysterol, whereas on the revised labels it is stated that 1 cc contains the equivalent of 1.25 mg of crystalline dihydrotachysterol.

Although we greatly regret that the new labeling has been confusing, there has been no qualitative or quantitative change in the composition of the product. Therefore, the dosage expressed in terms of a number of drops or of cubic centimeters is unaltered, but references to dihydrotachysterol by weight (i.e., in milligrams) require proportionate adjustment.

When Hytakerol in Oil was first made available for clinical use, it was honestly believed by chemists well versed in the mysteries of the sterols that the active constituent contained only dihydrotachysterol with virtually no admixture of other sterols. As a result of painstaking experiments in the course of years, dihydrotachysterol in pure crystalline form was recently isolated in minute amounts. Careful comparative studies then led to the conclusion that our preparation of dihydrotachysterol contains other relatively inert sterols formed during the process of irradiation.

The accompanying sterols of dihydrotachysterol are relatively inert from the standpoint of influencing the blood calcium level. They might be removed, but only with great difficulty and at prohibitive cost. Because of this, there has been no change in the product, but only in the labeling.

The situation with reference to Hytakerol is not unique nor anomalous. For example, Viosterol in Oil contains irradiated ergosterol (standardized in terms of vitamin D units determined by biologic test), which is actually a mixture of sterols. On the other hand, Drisdol (our crystalline vitamin D<sub>2</sub>) is a pure principle, produced at considerably higher—though not prohibitive—cost.

WINTHROP CHEMICAL COMPANY, INC.  
E. J. Foley, M.D.

170 Varick St.,  
New York City



# CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. Collaborators: E. B. ASTWOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLIN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

## PARATHYROID

ANDERSEN, D. H. AND R. R. SCHLESINGER.

Renal hyperparathyroidism with calcification of the arteries in infancy. *Am. J. Dis. Child.* 63: 101. 1942.

Renal hyperparathyroidism is rare in infants. Two cases are described in infants aged 6 and 4 weeks in whom the outstanding symptoms were tetany, twitchings and convulsions.

High phosphorus and non-protein nitrogen and acidosis were associated with low serum calcium in one and with normal content in the other child. The renal insufficiency was not apparent at first and was manifested chiefly by consistently low specific gravity of urine. The appearance of calcified arteries in roentgenograms stimulated further investigation of the urinary tract and discovery of congenital anomalies. The osseous lesions were never conspicuous. The essential postmortem findings in both cases were: severe renal anomaly, parathyroid hypertrophy, metastatic calcification of middle-sized arteries throughout the body and osseous lesions similar to those found in osteitis fibrosa. The differences between the picture in infancy, childhood, adolescence and adult life are described.—M.B.G.

## THYROID

LERMAN, JACOB and H. D. STEBBINS.

The pituitary type of myxedema. Further observations. *J. Am. Med. Assoc.* 119: 391. 1942.

The authors report an additional case of pituitary type of myxedema which when confirmed at autopsy was proven similar to the original case described by J. H. Means. Laboratory procedures indicated gonadal and adrenocortical hypofunction and absence of gonadotropic and diabetogenic substances of the pituitary.—C.P.

PONCHER, H. G., I. P. BRONSTEIN, H. W. WADE AND J. C. RICEWASSER.

Creatine metabolism in hypothyroid infants and children; further observations. *Am. J. Dis. Child.* 63: 270. 1942.

Determinations of the urinary output of creatine may serve as a valuable aid in the diagnosis of hypothyroidism, especially in infants and in older children when initial cholesterol levels are within normal limits and the osseous development is normal. At present biochemical and metabolic tests are not sufficient in themselves for the diagnosis of hypothyroidism or for the regulation of the dosage of thyroid.

The authors present a comprehensive discussion of the subject and describe the findings in six patients.—M.B.G.

## PANCREAS

WAGNER, R., P. WHITE AND I. K. BOGAN.

Diabetic dwarfism. *Am. J. Dis. Child.* 63: 667. 1942.

From a comparison of 200 diabetics with 159 non-diabetic children, the following conclusions are drawn:

1. While over height is characteristic of juvenile diabetes, stunting of growth occurs in 5 to 10% of diabetic children.

2. The weight-height relationship is normal in diabetic children except in some girls who have a specific form of obesity.

3. The onset of the sexual development of the average diabetic child with normal height and weight tends to occur precociously but sexual development does not progress at the normal rate. Retardation of sexual development is present in nearly all retarded diabetic children and disturbance in the appearance of secondary sex characteristics is more frequent than in non-diabetic children.

4. Dental caries is less frequent in diabetic than in non-diabetic children, but pyorrhea is more frequent.

5. Enlargement of the liver is common in diabetic children and adolescents.

6. Dwarfism. The diabetic child is most susceptible to retardation in growth from the twelfth to sixteenth year of life and from the second to sixth year of diabetes. Retardation in most girls has an earlier onset than in boys. Sexual development is delayed in every patient with dwarfism at the time of maximal retardation in height. The onset of retardation in growth in most cases occurs during the period of sexual development. Retardation of bone development is generally present. Arteriosclerosis, general and in the eye, is found in 47% and in 28%, respectively, of retarded diabetic children.

The incidence of the various etiological groups, according to the authors' classification of diabetic dwarfism is as follows: hypopituitary-like dwarfism, 50%; transitory infantilism, 27%; constitutional type, 12%; undernutrition, 2.5%; congenital anomalies, 2%; neglect, 1% and tertiary syphilis, 1%.

The best therapeutic results are obtained by the injection of anterior pituitary extract containing the growth hormone, 3 cc. every second day with thyroid substance, 1 to 3 grains a day by mouth. The highest insulin overbody weight quotients were found in the children treated with anterior pituitary extract and then in the thyroid treated group.—M.B.G.

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## Treatment of Simmonds' Disease

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IT HAS NOW been almost 30 years since Simmonds (1) described the syndrome associated with extensive pituitary destruction. Since then, there have been many reports of the various clinical and pathological manifestations of this disease (2). In a number of the reports, however, the clinical diagnoses are not well established. The diagnosis is sometimes difficult to make and has, not infrequently, been missed. Nevertheless, with the methods now available for study, the diagnostic accuracy has increased.

Although in this report we are chiefly concerned with the treatment of Simmonds' disease, we will also emphasize certain diagnostic features, since the proper understanding of these increases the efficiency of treatment.

The disease is always associated with marked destruction of the anterior pituitary gland. The cause of the destruction is varied, although most commonly it is postpartum necrosis (3) or a tumor. As a result of this destruction there is a marked decrease in the function of the thyroid, adrenals and gonads. Thus, properly to seek out this group of patients when there is marked disturbance of the function of one of these glands, one must carefully investigate the state of the other two. Although failure of the thyroid, adrenals or gonads usually develops simultaneously, in some instances the evidence is clear that the

onset of failure of the various functions may be separated by months or years.

We have listed below some of the clinical manifestations and tests which indicate hypofunction of the individual glands, realizing, of course, that some of these alterations are due to hypoactivity of several rather than of only one gland.

**Pituitary.** Local disturbances may be noted such as headaches, visual disturbances with demonstrable changes in the visual fields, enlargement and destruction of the sella turcica. These changes, however, are often absent. When the disease occurs in children, dwarfism is noted. The failure of the glands subsidiary to the pituitary is more manifest than the changes directly related to the pituitary.

**Thyroid.** All of the characteristics of primary myxedema may be present. In some instances, however, the basal metabolic rate may be much lower than the clinical state suggests. The basal metabolic rate is usually quite low, but it is sometimes normal, since at the time some patients are seen thyroid function has been preserved (case 3). The skin is sometimes smoother than normal. Generalized edema is usually present, although it is rarely sufficiently marked to permit pitting. The hair on the head may be of fine texture. The blood cholesterol tends to be slightly elevated. The plasma organic iodine is low. Bioassay of the urine for thyrotropic hormone reveals that none is present.

**Adrenals.** The cortical atrophy which results leads to the development of a clinical picture comparable to that of primary adrenal insufficiency.

**Asthenia** is one of the most common and pronounced manifestations. Mental changes frequently observed are depression, irritability and intolerance to pain. Hypoglycemic reactions develop at times. Not only does the general body hair decrease, but the axillary and pubic hair becomes scant or absent. In these patients we have never observed the type of pigmentation seen in Addison's disease. The blood pressure tends to be distinctly low and may drop further when the patient assumes an erect position. Mental disorientation or actual coma may be associated with the adrenal crises which sometimes develop. Anorexia, nausea, vomiting and abdominal cramps are apt to occur, particularly if infections are present, or if the patient is treated with thyroid.

The 17-ketosteroid excretion in the urine is markedly diminished, usually being less than 1 mg. per 24 hours (4). The serum sodium is definitely low in most cases, but in some instances, in order to demonstrate a disturbance of sodium metabolism, it is advisable to perform a sodium deprivation test such as the one described by Cutler, Power and Wilder (5, 6). The two procedures reported by Robinson, Power and Kepler (7) are useful and somewhat more simple than the foregoing test. These procedures depend upon the principle that patients with Addison's disease *a*), do not experience a normal diuresis following the rapid intake of a considerable quantity of water, and *b*), they tend to excrete excessive amounts of sodium chloride but retain urea. The serum potassium is sometimes elevated. The fasting blood sugar is occasionally low, but the defect in carbohydrate metabolism is best demonstrated by means of the insulin tolerance test. With this test one can almost invariably show insulin sensitivity and hypoglycemia unresponsiveness; i.e., in these patients there is a more marked fall in the blood sugar than in normal individuals and an impaired return to the fasting level (8).

**Gonads.** *a) Male.* There is loss of libido, impotence, scanty beard, decreased body hair, atrophy and weakness of muscles. The penis, testicles and prostate are small. The 17-ketosteroids are quite low and there is little or no follicle-stimulating hormone<sup>1</sup> in the urine. *b) Female.* There is loss of libido, sterility, amenorrhea (not associated with menopausal symptoms) and atrophy of the genitalia. The breasts are normal or small. Little, if any, follicle-stimulating hormone is present in the urine.

<sup>1</sup> When gonadal failure is primary, the 24-hour excretion of follicle-stimulating hormone in the urine is much greater than 10 R.U., but when the failure is on the basis of pituitary insufficiency, it is usually less than 10.

**General considerations.** Hypopituitarism may occur at any age, although most commonly during middle age; it is more common in females. An anemia is often present which does not respond to iron or liver. The condition is most frequently confused with anorexia nervosa, malnutrition with anemia or primary involvement of the subsidiary glands (thyroid, adrenals, gonads). We believe, however, that it can be accurately differentiated in most instances if studies are made and the data are considered collectively.

Not only has difficulty been encountered in the diagnosis of Simmonds' disease, but its treatment has been very unsatisfactory. Anterior pituitary extracts of various kinds, pregnant mare serum gonadotropin, thyroid, testosterone, adrenal cortical extract and many other substances have been used (2, 9, 10). The pituitary extracts usually have very little effect and usually produce an antihormone reaction. Of course, the use of pituitary extracts would seem to be the logical form of treatment, but since up to the present time they have failed, the next step is to use certain products of the subsidiary glands, (such as ovarian extracts and desiccated thyroid) hoping to secure a good balance between them. Thyroid, when given alone, usually does not cause much improvement and, indeed, not infrequently induces an adrenal crisis (9). It is not surprising that the symptoms of adrenal insufficiency become more obvious under thyroid treatment, since it promotes excretion of sodium and water (11, 12). This effect can be counteracted by the simultaneous utilization of sodium chloride and desoxycorticosterone, the exact amount necessary being assayed on each individual case. The implantation of pellets would seem advantageous because of convenience, efficiency and economy. From previous experience we have learned that some of these patients, after correction of the metabolic rate and of the water and electrolyte balance, still lack energy and strength. Consequently, since testosterone has been shown to cause a retention of sodium (13, 14), potassium (14, 15), nitrogen (15, 16, 17) and water, and since it increases the muscle mass (18) and strength, it seemed advisable to use it, in the form of pellets, in conjunction with the thyroid and adrenal treatment. Of course, in males it also tends to correct some of the gonadal disturbances. Testosterone in large doses causes elevation of the basal metabolic rate (19), but in doses of from 10 to 20 mg. daily does not affect it very much. Desoxycorticosterone acetate does not have an appreciable effect on the basal metabolic rate (20).

With these facts in mind, during the past year we have treated 5 unselected cases of Simmonds' disease with thyroid extract,<sup>2</sup> desoxycorticosterone acetate,<sup>3</sup>

<sup>2</sup> All of the thyroid used conformed to the U.S.P.

<sup>3</sup> The pellets of desoxycorticosterone acetate (Doca) were

sodium chloride and testosterone.<sup>4</sup> All patients were hospitalized. We give the case reports below.

#### CASE ABSTRACTS

**Case 1 (#1047166)** A housewife, aged 42, was admitted in May, 1941, because of myxedema. She had never been well since she had placenta previa with marked blood loss at the birth of her sixth child, 12 years previously. She was always pale and weak thereafter and never menstruated again, but had no hot flashes. A few months after delivery she became nervous, cried readily and later noted persistent drowsiness, sensitivity to cold, dry scaly skin, puffiness of face, hands and feet, loss of hair from axillae and pubis, thick speech, coarse voice and brittleness of nails. All teeth "just fell out." Occasional spells of nausea, vomiting and abdominal cramps occurred. The patient had taken thyroid extract for intervals of months for 10 years. Thyroid extract caused the basal metabolic rate to return to normal, yet the patient did not feel well, always lacking strength and energy. She occasionally had spells, unrelated to meals, when she developed weakness and faintness and sometimes nausea and vomiting. She also had other attacks which seemed to be hypoglycemic reactions, since they were characterized by weakness, nervousness, faintness and intense hunger and were readily relieved by the ingestion of food. For several years she had led an essentially vegetative existence.

On examination, the patient showed marked slowing of her mental and physical activities. The nutritional state was good, the weight 122 pounds (fig. 1). Her voice was coarse and low pitched, and the tongue thick. The skin was pale, dry, cool, scaly, puffy and inelastic. Hair on the head was fine and soft but thinned, eyebrows were sparse, there was no axillary or pubic hair. There was dorsal kyphoscoliosis. Breasts were normal. Genitalia were atrophic. Blood pressure was systolic, 90 and diastolic, 50 mm Hg.

Significant laboratory data were red blood cells 3,500,000, hemoglobin 71 per cent, white blood cells 2100, follicle stimulating hormone, negative to 10 R.U., 17 ketosteroids, 0.3 mg per 24 hours, basal metabolic rate, -43 per cent, blood lipids, 2400 mg per cent, cholesterol, 262 mg per cent, serum sodium, 133 m eq per liter (normal 140 to 142), serum potassium, 5.8 m eq per liter. Roentgenograms of the skull showed the sella turcica to be slightly smaller than normal. Plasma protein iodine was less than 1 microgram per cent (normal 4 to 8). Insulin tolerance test, marked sensitivity to insulin, the blood sugar falling to 28 mg per cent 30 minutes after the injection, intravenously, of 2 units of insulin (fig. 2). Urinary thyrotropic assay was negative. Gastric analysis showed no free acid in the fasting contents, even after the subcutaneous injection of 0.5 mg of histamine phosphate.

supplied through the kindness of Dr. E. Oppenheimer of the Ciba Pharmaceutical Products, Inc., Summit, N. J., and Dr. G. W. Thorn of the Peter Bent Brigham Hospital, Boston, Mass. Each pellet weighed approximately 125 mg.

<sup>4</sup> The tablets of methyl testosterone (Oreton M) and the pellets of testosterone (Oreton F) were supplied through the courtesy of Dr. M. Gilbert of the Schering Corp., Bloomfield, N. J. Each pellet weighed approximately 150 mg.

On June 11 she was given 1 cc, intramuscularly, of thyrotropic hormone.<sup>5</sup> Within an hour there was marked pallor, weakness and severe pain in the abdomen and neck. An intradermal test on the same day, using 0.1 cc of the same preparation, had been negative. Another preparation of thyrotropic hormone<sup>6</sup> given in intramuscular doses of 1 cc daily for a period of 2 weeks, had no definite effect on the basal metabolic rate. Intradermal



Fig. 1 Case 1. Note good nutritional state, myxedematous facies, normal breast and absence of hair.

sensitivity to a test dose of anterior pituitary extract<sup>7</sup> prevented its use in treatment.

On December 29, treatment was begun with sodium chloride, 5 gm daily, methyl testosterone, 10 mg three times daily, desoxycorticosterone acetate,<sup>8</sup> 2 mg daily,

<sup>5</sup> The thyrotropic hormone (antutrin T) was supplied by Parke Davis Co., Detroit, Mich.

<sup>6</sup> This preparation of thyrotropic factor was supplied by Armour Laboratories, Chicago, Ill.

<sup>7</sup> The anterior pituitary extract (Polysyn) was supplied by Armour Laboratories, Chicago, Ill.

<sup>8</sup> The desoxycorticosterone acetate (Doca) was supplied by Roche-Organon, Inc., Nutley, N. J.



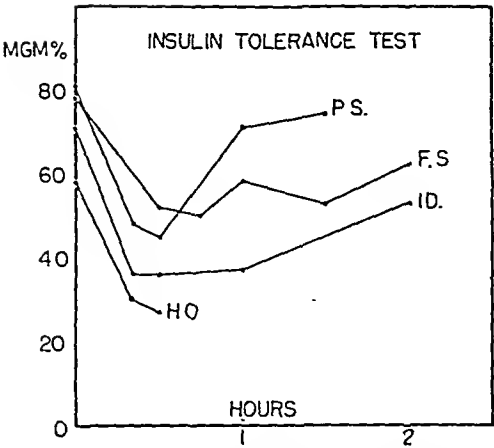


Fig. 2. RESPONSE OF BLOOD SUGAR FOLLOWING INJECTION OF 2 to 3 u of insulin intravenously. Note rapid fall in blood sugar and in two cases the hypoglycemic unresponsiveness.

intramuscularly; and thyroid, 0.5 grain daily. The dosages of these medications were varied in accordance with the clinical status of the patient and the significant laboratory

findings (fig. 3). At the time of discharge from the hospital (March 7), the patient possessed subcutaneous implantations of 2 pellets of testosterone and 1 of desoxycorticos- terone acetate. She was also taking thyroid, 1 grain daily, and sodium chloride, 2 gm. daily.

The patient demonstrated a marked increase in strength, energy and feeling of well-being. She stated that she felt distinctly better than she had for 12 years. She no longer had any complaints and the myxedematous manifestations disappeared (fig. 4). There was a moderate growth of hair in the axillae and pubis. The growth of hair on the head also increased.

We have examined her at frequent intervals during the past 4 months, since her discharge from the hospital, and have observed continued improvement and no ill effects.

Case 2 (#1047262). A white laborer, aged 46, was admitted to the hospital in August, 1941, complaining of weakness and dizziness. For 5 years he had noted gradually increasing weakness and fatigability. very scanty beard, impotence, lack of libido, slowing of mental and physical activities, sensitivity to cold and irritability. He

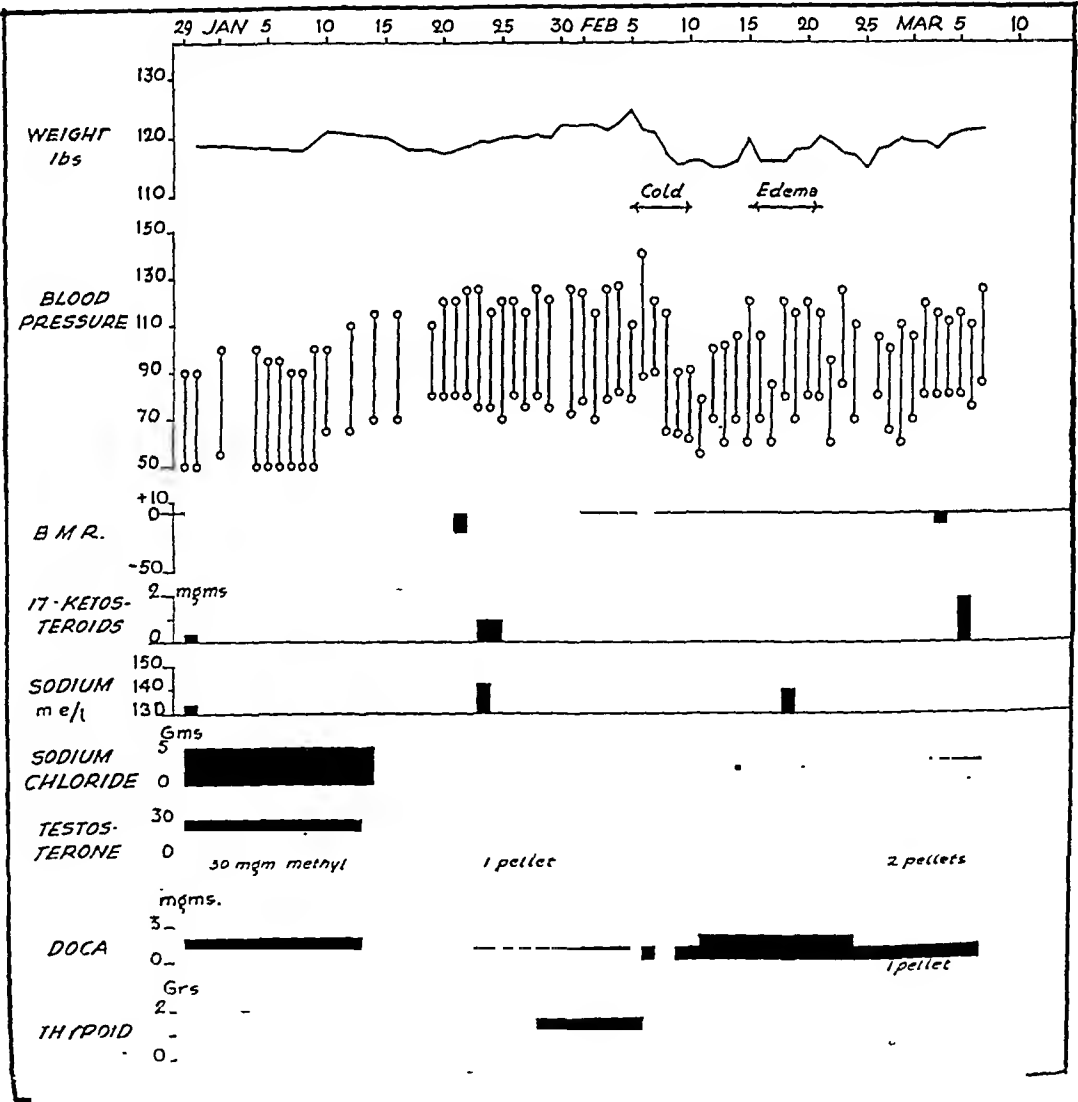


Fig. 3. RESPONSE TO TREATMENT IN case 1.



Fig 4 A Case 1 NOTE SIMILARITY OF FACE to that in primary myxedema  
B NORMAL APPEARANCE one month after beginning treatment

was treated with thyroid extract for 15 years with no appreciable benefit. Three months before admission, he noticed increased weakness and fatigability, with development of unsteady gait. Three weeks before admission the dosage of thyroid was increased to 2 grains per day. Shortly thereafter he developed marked weakness, nausea, vomiting, headache and blurred vision.

Examination showed a relatively good nutritional state, weight 171 pounds (fig 5), poor strength and slowing of the mental and physical activities. The skin was pale, pasty, smooth and cool, eyelids were puffy. There was no hair on chest, arms and legs and only a small amount on face, pubis and axillae. Penis, testicles and prostate were less than half of normal size. Blood pressure was 104 mm Hg systolic and 70 diastolic.

Laboratory examinations showed: Basal metabolic rate,  $-25$ , follicle stimulating hormone, negative to 10 R U per 24 hours, 17 ketosteroids, 2.5 mg per 24 hours. Bio assay of the urine for thyrotropic hormone was negative. Serum sodium was 127.4 m eq per liter and serum potassium 5.0 m eq per liter. Insulin tolerance test revealed increased sensitivity to insulin (fig 2). Roentgenogram of skull showed expansion and erosion of the sella turcica. Visual fields were normal. Roentgen treatment to the pituitary (200 roentgen units every 2 days for 20 days), given from September 5 to 30, resulted in no definite improvement. Nausea and vomiting were very troublesome during the course of treatment, in spite of the administration of yeast, nicotinic acid and sodium chloride.

In the succeeding 3 months there was a distinct increase in weakness, mental depression, anorexia, nausea and vomiting. Basal metabolic rate fell to  $-36$  per cent. Blood pressure fell to 74 mm Hg systolic and 56, diastolic.



Fig 5 Case 2 GOOD NUTRITIONAL STATE myxedematous facies

A polyvalent anterior pituitary extract<sup>7</sup> was given in doses of 1 cc. three times daily, intramuscularly, from December 4 to 18, but no beneficial effects were noted.

On December 26, treatment was begun with sodium chloride, 5 grams daily; thyroid extract, 0.5 grain daily; methyl testosterone, 10 mg. three times daily; and desoxycorticosterone acetate,<sup>8</sup> 2 mg. daily (fig. 6). It was necessary to raise the dosage of thyroid to 2 grains daily. At the time of discharge (March 6) he possessed subcu-

Case 3 (#1048285), a female artist, aged 37, was admitted in May, 1941, complaining of headaches and blurred vision. She had had a 'nervous breakdown' 10 years previously with subsequent irritability and slight-depression, and 5 years later (1936) developed a few attacks of asthma. At about the same time the menses ceased and did not recur; there were no hot flashes. During the year preceding admission she noted easy fatigability, weakness, sensitivity to cold, dryness of hair, head-

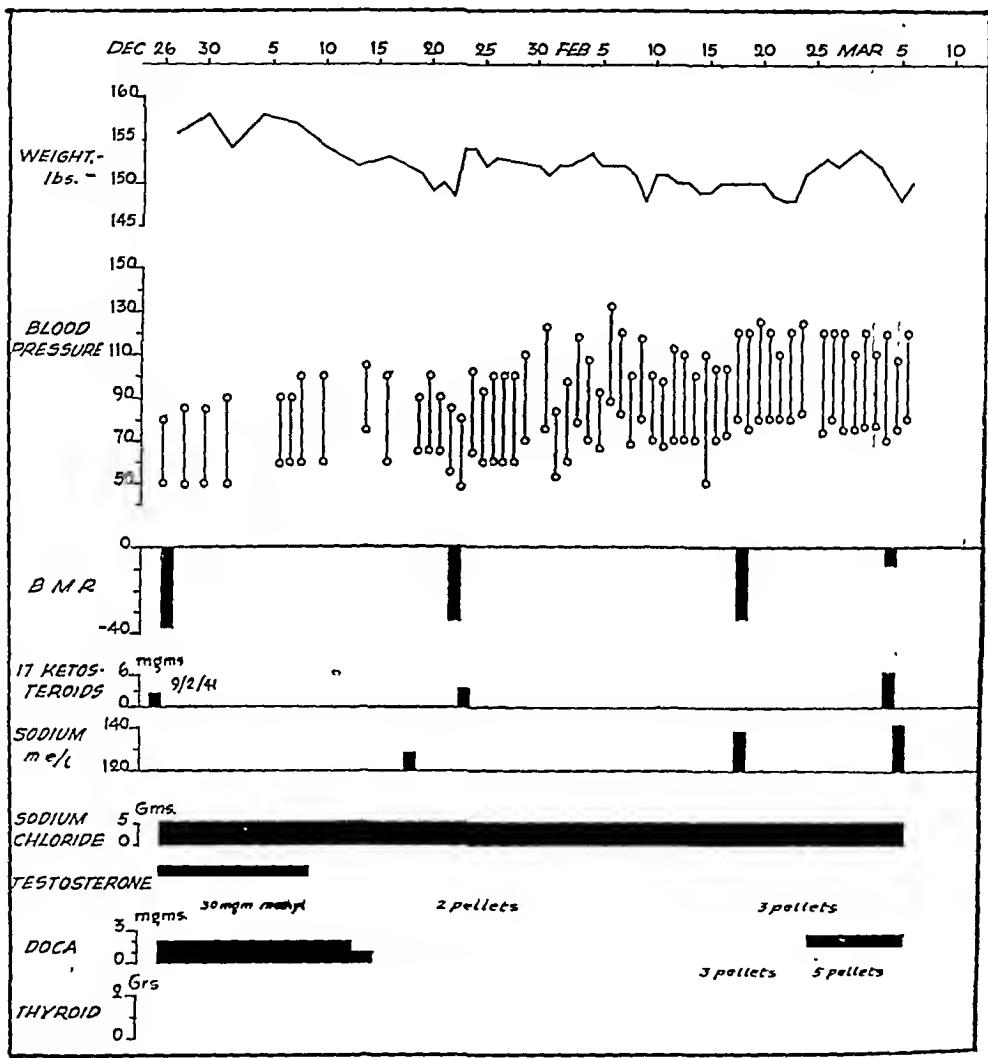


Fig. 6. RESPONSE TO TREATMENT IN case 2.

taneous implantations of 5 pellets of desoxycorticosterone acetate and 3 of testosterone. The blood pressure, basal metabolic rate and serum sodium returned to normal levels. The patient changed from a weak, constantly complaining, depressed individual to one who was active and strong. He developed a heavy growth of hair over the body. The penis, testes and prostate increased in size. His strength and libido increased so much that he was having coitus 3 times a week.

He has been seen at 2 to 3-week intervals for the past 3 months. The added salt was discontinued because the blood pressure was slightly elevated; following the decrease in salt intake the pressure returned to normal.

ache and blurring of vision. Her weight did not vary.

On examination she was found to be a weak individual, somewhat insensitive to psychogenic influences, but hypersensitive to pain. General nutrition and development were relatively good (weight, 118 pounds). Skin was pale, dry, scaly and cool; eyelids were puffy. Hair was fine and dry; it was scanty on pubis. In the left eye visual acuity was much impaired and the optic disc was pale; visual field determination revealed bitemporal hemianopsia. Blood pressure was 90 mm. Hg. systolic and 60, diastolic.

Laboratory studies revealed: Red blood cells 5,000,000; hemoglobin, 97 per cent; white blood cells 6400. Fasting blood sugar, 87 mg. per cent; blood chlorides, 99 m. eq.

per liter Basal metabolic rate, -9 per cent Roentgen ray examination of skull showed marked depression and erosion of the floor of the sella, erosion and posterior displacement of the posterior clinoidal processes

A diagnosis of chromophobe adenoma was made and roentgenotherapy applied, 200 roentgen units daily for 20 days She was discharged in June, but was readmitted in August because no improvement resulted Nausea and vomiting occurred at intervals The results of examination

return to the hospital a further decrease in visual fields was found The blood pressure was 90 mm Hg systolic and 60, diastolic, red blood cells, 3,700,000, hemoglobin, 72 per cent, white blood cells, 5700, serum sodium, 128 m eq per liter, serum potassium, 4.3 m eq per liter, and basal metabolic rate, -30 per cent

Daily administration of 10 gm of sodium chloride caused only slight improvement in her condition She was so weak that she remained in bed all of the time and was

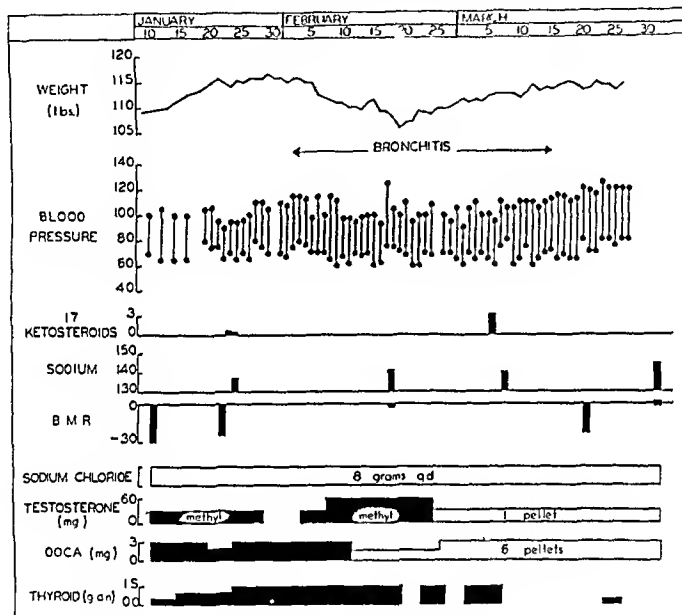


Fig. 7 RESPONSE TO TREATMENT IN CASE 3

were the same as in May, except that the disturbances were slightly more marked. The serum sodium was 132 m eq per liter, 17 ketosteroids, 0.4 mg per 24 hours, follicle stimulating hormone, negative to 10 m u, basal metabolic rate, -10 per cent. Another course (4000 roentgen units) of roentgenotherapy was given over the pituitary. Weakness, nausea and vomiting became pronounced. The blood pressure remained at a lower level and upon one occasion dropped to 60 mm Hg systolic and 40, diastolic, with general symptoms of shock.

She was then treated daily with 5 gm of sodium chloride and with from 4 to 6 mg of desoxycorticosterone acetate. Definite improvement in the clinical state resulted and the serum sodium returned to normal levels, but she continued to be weak. She remained at home from October 4 until November 30, taking salt but no hormone. Weakness, dizziness and headache persisted and occasionally she had nausea and vomiting. Upon her

fed by the nurses. On January 9, treatment was begun with sodium chloride, 8 gm daily, methyl testosterone, 10 mg 3 times daily, desoxycorticosterone acetate, 3 mg daily, intramuscularly, and thyroid, 0.5 grain daily (fig. 7). Within a few days the anorexia, nausea and vomiting disappeared. There was so much increase in strength and energy that the patient began to exercise a great deal in the ward and experienced a feeling of well being for the first time in several months. Gain in weight was rapid. Because of the persistence of hypothyroid symptoms and a low basal metabolic rate, the dosage of thyroid extract was increased to one grain daily. The dosage of desoxycorticosterone acetate was reduced to 2 mg daily, but an associated fall in blood pressure made it necessary to resume the original dose. With cessation of the methyl testosterone for 6 days there was a definite loss of energy and strength. Associated with the development of a marked bronchitis there was a drop in the blood pressure,

loss of weight and a partial return to the previous clinical state. With the disappearance of infection she showed remarkable improvement. The thyroid was temporarily discontinued since it was thought to be a factor in the persistence of a low-grade fever. Liver extract,<sup>9</sup> 1 cc. daily for 3 days, caused no appreciable change in the blood picture, but at the time of discharge the hemoglobin was 85 per cent, red blood cells 4,100,000 and hematocrit 36.5 per cent. She was finally regulated with sodium

body, lasting only a few days. Menses ceased 10 years previously (1924) without hot flashes or other menopausal symptoms. She was known to have had a normocytic anemia of undetermined etiology for 7 years.

Physical examination demonstrated normal size and development (weight 117 pounds); dry, inelastic, atrophic, cool skin; scanty growth of hair on pubis, axillae and eyebrows; thin, brittle, spoon-shaped nails; and a blood pressure of 140 mm. Hg. systolic and 70, diastolic.

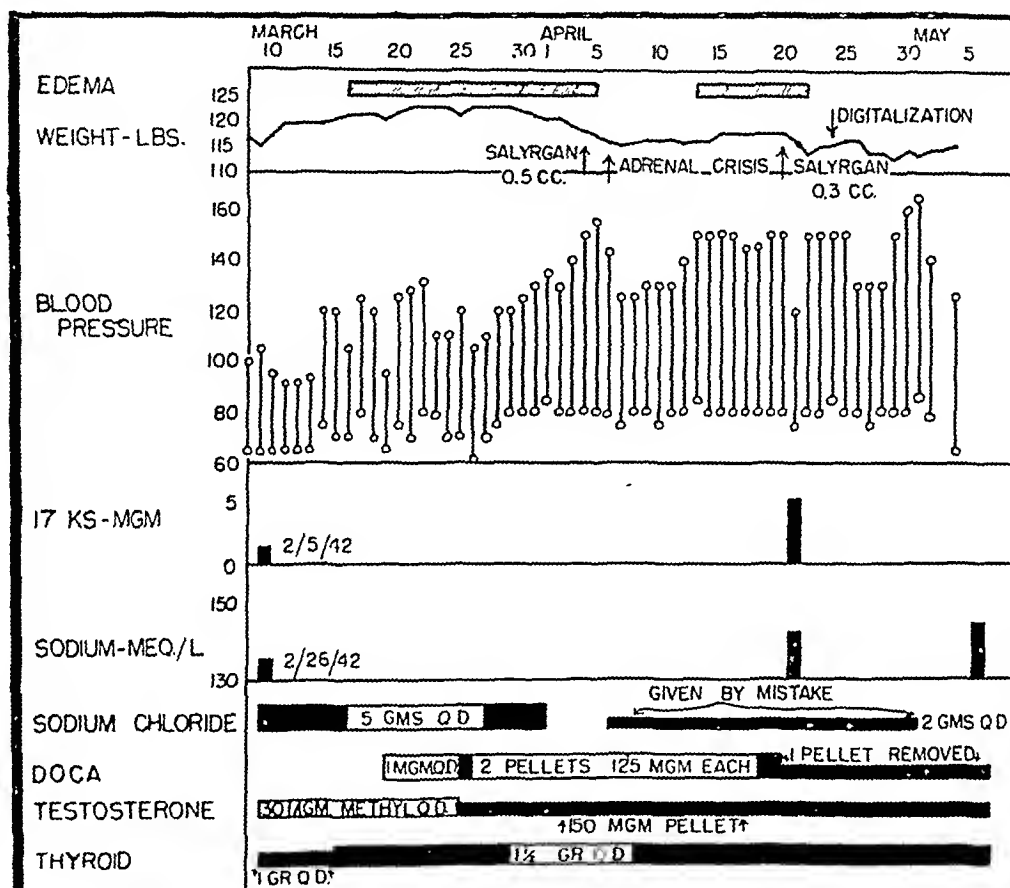


Fig. 8. RESPONSE TO TREATMENT IN case 4.

chloride, 8 gm. daily, 1 pellet of testosterone, 6 pellets of desoxycorticosterone acetate and thyroid, 0.5 grain daily. With this regimen the strength and general feeling were excellent and the blood pressure, sodium and basal metabolic rate were normal. She was discharged April 1. When seen again in May the progress had been excellent. There remained marked narrowing of the visual fields. Resection of the tumor was recommended, but the patient felt so well that she refused.

**Case 4 (#105888).** A single white woman, aged 60, was admitted to the hospital in 1934, complaining of shortness of breath on exertion. Eight weeks before admission she noticed a sensitivity to cold weather and soon thereafter loss of appetite, weakness, dizziness, falling of hair and exertional dyspnea. Three weeks before admission she developed anesthesia of the left side of the

The red blood cell count was 3,500,000; hemoglobin, 69 per cent; reticulocytes, 0.6 per cent; hematocrit, 39 per cent; cholesterol, 247 mg. per cent; basal metabolic rate, -20 per cent. No free acid in gastric juice even after the injection of 0.5 mg. of histamine.

No appreciable change in the hemoglobin, red blood cells or reticulocytes followed intensive treatment with iron, liver and thyroid. With 3 grains daily of thyroid for 5 weeks there was no change in the blood counts. The basal metabolic rate rose to -7 per cent, but the patient experienced several attacks of anorexia, nausea, vomiting, abdominal cramps and diarrhea. The weight dropped from 115 to 106 pounds and the blood pressure dropped to 105 mm. Hg systolic and 70, diastolic. For the next 6 years she took thyroid irregularly, but never felt very well. She was bothered at times with sensitivity to cold, anorexia, nausea, vomiting, abdominal cramps, weakness, dizziness, headaches and occasional angina pectoris.

She was readmitted to the hospital in January, 1942.

<sup>9</sup> The liver extract (Reticulogen) was supplied by Eli Lilly & Co., Indianapolis, Ind.

complaining chiefly of anorexia, weakness, dyspnea and edema. The findings in the physical examination were similar to those in 1934.

The red blood cell count was 4,200,000, hemoglobin, 68 per cent, basal metabolic rate -33 per cent, 17-ketosteroids, 1.4 mg per 24 hours, follicle stimulating hormone, negative to 20 R.U. The insulin tolerance test showed hypersensitivity to insulin, with an impaired hypoglycemic response (fig 2). The protein iodine was 3 micrograms per cent, serum sodium 135.6 m eq per liter. In roentgenograms the sella turcica appeared normal.

On March 9, 1942, treatment was started with daily doses of 5 gm of sodium chloride, 30 mg of methyl testosterone and 1 grain of thyroid extract (fig 8). Within a few days there was an increase in strength and in blood pressure. Slight edema of the ankles developed, but the patient had had this occasionally before treatment. At times the blood pressure was low, so 1 mg of desoxycorticosterone acetate per day was given. On March 25, 2 pellets of desoxycorticosterone acetate and 1 of testosterone were implanted. The blood pressure continued to rise, the edema increased and rales appeared over the lower half of the chest. Discontinuance of the extra salt did not have much apparent effect, so 0.5 cc of salyrgan was given. The edema disappeared, but there was an adrenal crisis (drop of blood pressure, nausea, vomiting, diarrhea, abdominal cramps and marked weakness). Within a few days the edema and elevated blood pressure again returned. One pellet of desoxycorticosterone acetate was removed. The administration of 0.3 cc of salyrgan again caused disappearance of the edema and a drop in blood pressure, but these changes were only transitory. A similar response occurred with digitalization. On April 30 it was discovered that, by mistake, she had been receiving 2 gm of added salt daily for the preceding 3 weeks. When this was stopped the blood pressure returned to normal and no more edema developed, in spite of the discontinuance of digitalis.

At the time of discharge from the hospital the patient was receiving 1.5 grains of thyroid per day and had implantations of 1 pellet of testosterone and 1 of desoxycorticosterone acetate. At this time the blood pressure, basal metabolic rate, serum sodium and 17-ketosteroid excretion and blood counts were normal. During her stay in the hospital she experienced marked improvement. There was a distinct increase in strength, energy and ambition and she had no more complaints. A very slight beard appeared, but this had not been noticed by the patient.

When seen again, 2 weeks later, the blood pressure was 160 mm Hg systolic and 90, diastolic, 4 weeks later it was 185 mm Hg systolic and 95, diastolic. No edema had developed and there was no gain in weight, but she had been bothered with headaches, slight exertional dyspnea and orthopnea. The pellet of desoxycorticosterone acetate was removed on June 5, following this the blood pressure became normal and she felt well in every way.

Case 5 (#764228) F.S., aged 45, was admitted to the Evans Memorial Hospital<sup>10</sup> (#286299) December, 1941,

in a confused state. She had not felt very strong for about 20 years, following a pnhysterectomy for a pelvic inflammatory disease. She was admitted to the Boston City Hospital in 1934, complaining of pronounced weakness, easy fatigability, drowsiness and weight loss of 2 years' duration. She had had occasional spells of anorexia, nausea and vomiting. On one occasion her family physician found a blood pressure of 84 mm Hg systolic. Examination, in 1934, showed pallor of skin, slowing of mental and physical activities, scoliosis, hyperactive deep reflexes and equivocal Babinski reactions. The red blood cell count was 3,000,000, hemoglobin, 60 per cent, hematocrit, 28 per cent, mean corpuscular volume, 90 cubic micra. Kahn, doubtful. Follicle stimulating hormone, negative. Glucose tolerance test, using 100 grams of glucose by mouth fasting 79 mg per cent, 30 minutes, 103, 1 hour, 105, 1.5 hours, 107, 2 hours, 111. The basal metabolic rate was -21 per cent. Gastric analysis revealed no free acid in fasting contents.

Adequate doses of iron, liver and thyroid caused no appreciable change in the blood picture. The basal metabolic rate returned to normal levels, but no improvement in the clinical state occurred. In association with the treatment with thyroid she developed an increase in the pulse rate, a drop in blood pressure and nausea, vomiting and diarrhea.

During the subsequent 8 years weakness and fatigue remained prominent. Two weeks preceding admission she developed nausea and often vomited, diplopia also appeared. On the day before admission she was disoriented as to time and place.

Examination revealed a fairly good general state of nutrition (weight 122 pounds) and development, clouded sensorium, slurred speech. The skin was pale, dry, smooth and atrophic. Hair was dry, no hair on arms or legs, the hair in axillae, on pubis and eyebrows was sparse. There was marked dorsal kyphosis. There was slight weakness of the muscles supplied by the left sixth and seventh nerves, bilaterally positive Babinski, Oppenheim, Chaddock and Gordon signs, hyperactive reflexes of extremities, spasticity of legs. Breasts were normal. Blood pressure was 108 mm Hg systolic and 76, diastolic. There was slight edema of the legs.

The laboratory studies revealed that the blood picture was the same as before, basal metabolic rate, -32 per cent, hippuric acid, 1.2 gm, Hinton test on serum and spinal fluid, positive, protein of cerebrospinal fluid increased but no increase in cells. The water test (7) for adrenal insufficiency was positive, but the Wilder test (5) was negative. The insulin tolerance test (3.5 U intra-venously) showed a hypoglycemic unresponsiveness (see fig 2). At the end of 1 hour there was marked sweating, drowsiness, fatigue and mental confusion. The test for follicle stimulating hormone was negative, 17-ketosteroids, 0.2 mg per 24 hours, serum sodium 127 m eq per liter, cholesterol, 167 mg per cent. Roentgenograms of the skull showed that the sella turcica was small, but otherwise normal. There was decalcification and kyphosis of the dorsal spine.

On January 9, treatment was begun with thyroid, 0.5 grain daily. The dosage was progressively increased until

<sup>10</sup> The authors are indebted to Doctors Keefe, Moss and Oliver for the opportunity of following the course of this patient.

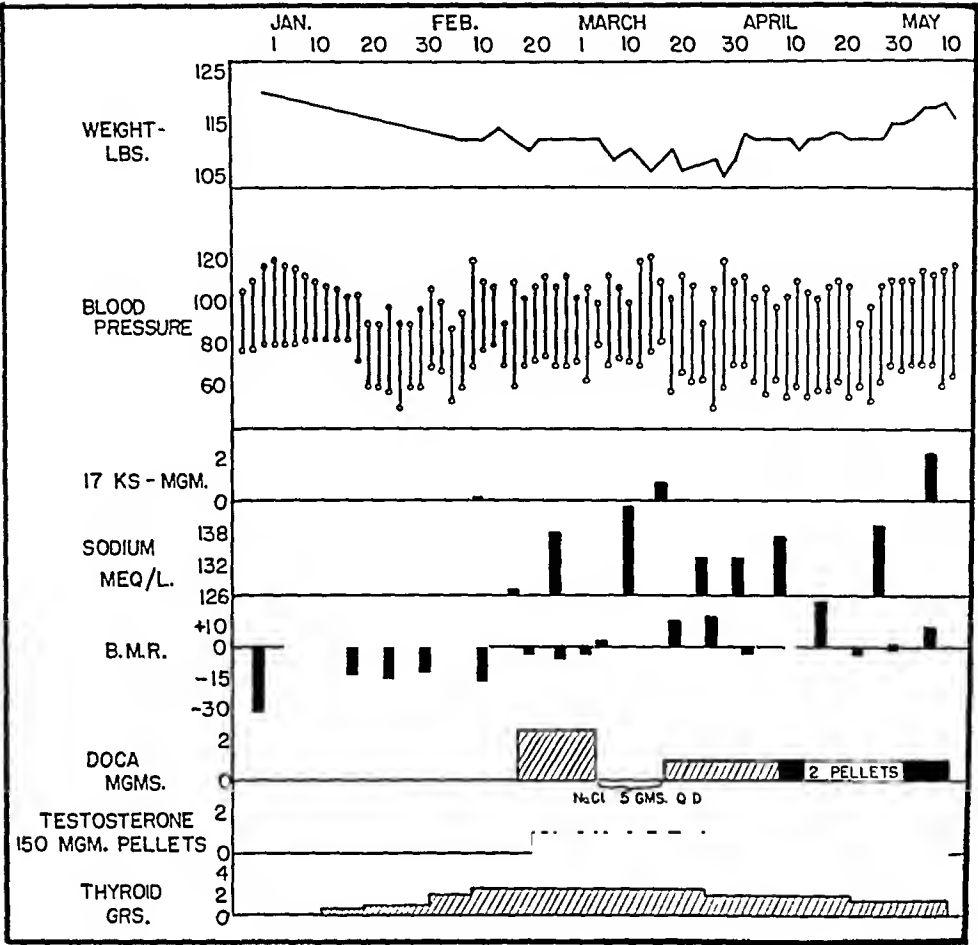


Fig. 9. RESPONSE TO TREATMENT IN case 5.

2.5 grains per day were given. With this treatment there was a rise in the basal metabolic rate to normal, but there was a distinct fall in weight and blood pressure and no improvement in the patient. She was finally regulated with subcutaneous implantations of 2 pellets of desoxycorticosterone acetate, 2 pellets of testosterone and 1.5 grains of thyroid by mouth per day (fig. 9). At the time of discharge (May 12) the blood pressure, serum sodium and basal metabolic rate were normal. The patient had experienced a marked increase in strength. She felt well in every way and had no complaints. The slight anemia persisted. No excess of hair growth occurred.

DISCUSSION OF CASES

Clinical Characteristics

*History.* Of the 5 patients treated, there were 4 females and 1 male, with ages ranging from 37 to 60 years (table 1). At the time that we were consulted, these patients had had their disease for intervals of 5 to 20 years. None of the patients had had any sexual activity for several years. The females had had amenorrhea for a long time but none had experienced menopausal reactions. All had clear-cut symptoms of

TABLE 1. SIGNIFICANT CLINICAL DATA ON PATIENTS WITH SIMMONDS' DISEASE

| Case No. | Etiology            | Age years | Sex | Duration of Symptoms years | Sex Activity | Hot Flashes | Blood Pressure, mm. Hg | Adrenal Crisis | Myxedema |
|----------|---------------------|-----------|-----|----------------------------|--------------|-------------|------------------------|----------------|----------|
| 1        | Postpartum necrosis | 42        | F   | 12                         | o            | o           | 90/50                  | +              | +        |
| 2        | Chromophobe adenoma | 46        | M   | 5                          | o            | o           | 74/65                  | +              | +        |
| 3        | Chromophobe adenoma | 37        | F   | 5                          | o            | o           | 90/60                  | +              | +        |
| 4        | ? Thrombosis        | 60        | F   | 8                          | o            | o           | 100/65                 | +              | +        |
| 5        | ? Syphilis          | 45        | F   | 20                         | o            | o           | 105/75                 | +              | +        |

myxedema. Four had been diagnosed as having myxedema and had received thyroid treatment irregularly for several years. In association with this treatment, each had experienced attacks of anorexia, nausea, vomiting and weakness. Abdominal cramps and diarrhea were sometimes present and one patient became totally disoriented. In none of the cases was either the patient or the physician satisfied with the thyroid treatment. There was a response in the basal metabolic rate, but the patient would not feel very well and therefore took the thyroid very irregularly. Three patients experienced symptoms of marked adrenal insufficiency even without thyroid treatment. Three had had spontaneous hypoglycemic reactions. All were bothered with weakness and lack of energy. Two patients had gained weight in the course of the disease, 2 had remained of the same weight and 1 had lost a small amount. All tended to be depressed and irritable and none had done more than a trivial amount of work for a long time. Three had been found to have anemia several years previously, and had taken iron and liver without benefit.

**Physical examination.** Contrary to the usually emphasized chief characteristic of this disease, cachexia, none of our patients was cachectic. Furthermore, in only 1 of the 8 other cases of Simmonds' disease whom we have studied, was this manifestation present. The general nutritional state appeared relatively good (fig. 1, 5). In 2 patients the changes of myxedema were classic (fig. 4, A), whereas in the others they were present although not so marked. In all, the skin was cool and puffy. In 3 it was rough, but in the other 2 it was smoother than in normal individuals. The hair on the head was slightly thin and fine. There was little, if any, axillary or pubic hair, and essentially no

136 m eq per liter (normal 140 to 142). The excretion of 17 ketosteroids in the urine was quite low (0.2 to 2.5 mg per 24 hours). No follicle-stimulating hormone was found in the urine, tested for 10 R.U. in 4 cases, for 20 R.U. in 1 case. The insulin tolerance test, performed with 4 patients, using from 2 to 3 U of insulin intravenously, showed an insulin sensitivity

TABLE 3 TREATMENT WHEN DISCHARGED FROM HOSPITAL

| Case No | Thyroid, gr | Testosterone, 150 mg pellets | Desoxycorticosterone Acetate, 125 mg pellets | NaCl, gm q d |
|---------|-------------|------------------------------|--|--------------|
| 1       | 1           | 2                            | 1  | 3            |
| 2       | 2           | 3                            | 5  | 0            |
| 3       | 3           | 1                            | 6  | 8            |
| 4       | 1½          | 1                            | 1  | 0            |
| 5       | 1½          | 2                            | 2  | 0            |

and in 2 there was an impaired hypoglycemic response. Roentgenograms of the skull revealed in 2 subjects changes in the sella turcica, interpreted as being due to a pituitary tumor.

#### Treatment

**Regulation of medication.** As may be seen on the individual charts of the cases of the patients (fig. 3, 6, 7, 8 and 9), the adequate regulation of the doses of the various hormones is attained only after careful and prolonged observation of the patients. Most of the difficulty encountered is in the estimation of the number of pellets of desoxycorticosterone acetate which are necessary, because it sometimes takes several weeks to note their full effect. Desoxycorticosterone acetate in oil was used in conjunction with the thyroid and testosterone. The amount of desoxycorticosterone acetate necessary to maintain a normal weight, blood pressure and blood serum was regarded as the adequate quantity. We attempted to give enough desoxycorticosterone so that only a small amount of extra salt was necessary. Thereby, the patient would be prepared for respiratory infections or any other added burdens by merely increasing his ingestion of salt. The effects of respiratory infections may be noted in cases 1 and 3. At the time of discharge the number of pellets of desoxycorticosterone acetate used varied from 1 to 6, 125 mg each (table 3). One patient was discharged with instructions for taking 3 grams of salt daily, another was taking 8 grams daily, while none was prescribed for the other three.

The amount of thyroid necessary was a much more simple problem. The initial dose of thyroid was 0.5 grain and this was increased until, by clinical observation and according to the basal metabolic rate, there was no evidence of thyroid insufficiency. The

TABLE 2 SIGNIFICANT LABORATORY STUDIES IN PATIENTS WITH SIMMONDS' DISEASE

| Case No | BMR % | FSH | 17 Ketosteroids mg/24 hr | Serum Sodium m.e. per liter | X ray of Sella |
|---------|-------|-----|--------------------------|-----------------------------|----------------|
| 1       | -43   | 0   | 0.3                      | 133                         | Negative       |
| 2       | -36   | 0   | 2.5                      | 127                         | Tumor          |
| 3       | -30   | 0   | 0.4                      | 127                         | Tumor          |
| 4       | -33   | 0   | 1.4                      | 136                         | Negative       |
| 5       | -32   | 0   | 0.2                      | 127                         | Negative       |

hair on the trunk. There was no atrophy of the breasts. The internal and external genitalia were atrophic. The blood pressure ranged from 76 to 105 mm Hg systolic, and from 65 to 75, diastolic.

**Laboratory studies.** The basal metabolic rate was -30 per cent, or below, in each case (table 2). The plasma organic iodine, determined in 2 cases, was found to be in the range characteristic for myxedema. No thyrotropic hormone was found in the urine of 2 subjects. The serum sodium ranged from 127 to



ultimate dosage varied from 0.5 to 2 grains. The more the thyroid was increased, the more the desoxycorticosterone acetate had to be increased.

With the females the aim as regards the use of testosterone was to use enough to secure a marked increase in strength, energy and general well-being without obtaining masculinization. This usually required 1 or 2 pellets (150 mg. each). The dosage for the male was governed not only by these general reactions but also by the amount of sexual stimulation. Three pellets were required in his case.

Each of the patients was given small amounts of food between meals and at bed-time in order to distribute the supply of carbohydrates evenly over the 24 hours, thereby preventing hypoglycemic reactions.

*Results of treatment.* In all 5 cases the blood pressure, basal metabolic rate and serum sodium have returned to normal and have remained there. The myxedematous manifestations have disappeared. In each subject there has occurred a marked increase in strength, energy and ambition. The mental state has changed from a dull, irritable and depressed level to an alert and cheerful one. All have developed a marked increase in the desire and the capacity for work. None of the symptoms of adrenal insufficiency has reappeared. The 17-ketosteroid excretion increased in each case, varying from 2 to 6 mg. per 24 hours. The weight curves varied somewhat, but had a tendency to increase with the institution of treatment. There were counterbalancing actions of the drugs, however, the thyroid promoting loss of weight in part by its diuretic action, whereas the testosterone and desoxycorticosterone acetate promoted gain in weight due to the retention of water and sodium and to the increase in muscle mass.

Of the 3 patients with normocytic and normochromic anemia, none of whom had responded to iron or liver, the anemia has disappeared in two. If this response is directly related to the hormone treatment, it possibly is due to the testosterone, since thyroid had been tried previously without benefit.

The 60-year-old woman described in case 4 did not tolerate very much desoxycorticosterone acetate, reacting with slight hypertension and edema. There is very good evidence, however, that she had adrenal insufficiency. She had previously had attacks of angina pectoris with mild cardiac failure. Therefore, it is our impression that the adrenal insufficiency tended to prevent her from having cardiac failure, but when this was corrected the latter became apparent.

In no case was there enough overgrowth of hair to cause concern.

#### SUMMARY

Five cases of Simmonds' disease have been treated with desoxycorticosterone pellets, testosterone pel-

lets and thyroid. The results have been gratifying in each case. In each there was a marked increase in strength, energy and feeling of well-being. The blood pressure, basal metabolic rate and serum sodium returned to normal. No significant ill-effects resulted from the treatment.

The dosage of the various substances must be determined individually in each case.

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acetate, no other medication was used until 10 days following the last dose.

Patients were allowed the freedom of the wards throughout the experimental period, so that a reasonably normal activity level could be maintained. However, fluid intake and output were carefully measured by a triple check, the patient, the ward attendant and the nurse each making separate measurements before discarding the specimen. Care was taken that diet from an extraneous source was not used. Inasmuch as 2 of these patients, upon whom most of the studies were performed, were desirous of working

not determined in the present series of observations. Respiratory and fecal water and the water of insensible respiration were not estimated, but were believed to be reasonably constant throughout the period of study, as none of the patients suffered from diarrhea nor had any evidence of unusual sweating from activity during the experiment.

RESULTS

*Water-restriction tests.* At the end of periods of low-salt intake (1.5 to 3.9 gm. daily) and normal or high-salt feeding (12 to 30 gm. daily), respectively,

TABLE 1. EFFECTS OF VOLUNTARY RESTRICTION OF FLUID INTAKE ON URINARY OUTPUT AFTER LOW AND HIGH NORMAL SODIUM CHLORIDE FEEDING

| Patient | Approximate Daily Intake of Sodium Chloride |            | Test Period (hr.) | Fluid Intake, cc. | Urine Output, cc. | Comment   |
|---------|---|------------|-------------------|-------------------|-------------------|---|
|         | No. days prior to test                      | Amount gm. |                   |                   |                   |   |
| J.W.    | 8   | 3.5        | 24                | 1500              | 7000              | Headache toward end of period   |
| J.W.    | 13  | 15.0       | 9                 | 1500              | 8550              | Severe headache, faintness; temp. 101° F. Immediately after test ended drank 2500 cc. water |
| C.A.    | 3   | 1.5        | 6                 | 750               | 1700              | Drank 700 cc. water at end of test period   |
| C.A.    | 3   | 12.0       | 6                 | 740               | 2400              | Thirst intense; bolted out of bed to drink 1680 cc. water                                   |
| H.O.    | 12  | 3.9        | 24                | 2520              | 3550              | Increased temp., sweating, nausea, vomiting, abdominal pain                                 |

and yet were unable to keep a job because of the polydipsia and polyuria, there was little or no tendency to cheating.

The determination of sodium in the blood and urine was made by the method of Darnell and Walker (2); that of potassium in the same fluids, by the procedure of Drekter (3), in which silver cobaltic nitrate instead of cobaltic nitrate is used as a precipitating agent, and colorimetric estimation is substituted for permanganate titration. Urinary chlorides were estimated by the method of Wilson and Ball (4) with special care for the preservation and periodic re-standardization of reagents.

Salt-loading tests were performed as follows. After the patient had been on the standard diet for at least 3 days, he was given in lieu of breakfast, on the morning of the test, 0.25 gm. of sodium chloride per kg. of body weight as a 10 per cent aqueous solution. Blood and urinary determinations of sodium and chloride were performed just before beginning the test and at hourly intervals up to 5 hours following the ingestion of salt.

Fluid intake and urinary output were carefully measured. As a result of previous investigation, dietary water was found to vary little, and thus was the patient was placed on a regime of water restric-

tion. Results are recorded in table 1. In all patients following a low-salt regime, the test period of 24 hours could be completed, but not without distressing symptoms.

Six hours after restricting the intake of water in patient C. A., who for several days previously had utilized a diet high in salt, symptoms of shock occurred which were sufficiently severe to necessitate stopping the test. At the patient's request, a similar 6-hour period of water deprivation was used after a low-salt intake, at the end of which time the patient was very uncomfortable and was apprehensive lest he feel as distressed as on the preceding occasion. Patients C.A. and J.W. showed a severe water deficit with urinary output far in excess of fluid intake (table 1). The primacy of the polyuria coupled with the behavior following the administration of a single large dose of salt definitely places these cases in the category of the syndrome of diabetes insipidus commonly seen.

The third case, H.O., responded to reduced fluid intake by a markedly reduced urinary volume not greatly beyond that of the fluid intake. A rise in temperature, profuse sweating, nausea, vomiting, and severe abdominal pain were induced as the fluid restriction was continued. The test was repeated sev-

TABLE 2 EFFECTS OF ADMINISTERING 0.25 GM. OF NaCl IN A 10 PER CENT AQUEOUS SOLUTION PER KILOGRAM OF BODY WEIGHT

| Subject | Hourly Determinations of                       |     |     |     |     |     |                                 |     |      |      |     |     |                    |      |      |      |      |      |
|---------|--|-----|-----|-----|-----|-----|---------------------------------|-----|------|------|-----|-----|--------------------|------|------|------|------|------|
|         | Blood serum chloride as NaCl,<br>mg per 100 cc |     |     |     |     |     | Urinary                         |     |      |      |     |     |                    |      |      |      |      |      |
|         |  |     |     |     |     |     | Chloride as NaCl,<br>mg per min |     |      |      |     |     | Output, cc per min |      |      |      |      |      |
|         | 0  | 1   | 2   | 3   | 4   | 5   | 0                               | 1   | 2    | 3    | 4   | 5   | 0                  | 1    | 2    | 3    | 4    | 5    |
| Normal  | 570  |     | 620 | 655 |     | 580 | 6.0                             | 7.2 | 10.3 | 18.2 | 9.0 | 9.0 | 1.0                | 1.2  | 1.7  | 2.4  | 1.8  | 1.0  |
| C A     | 590  | 620 |     | 635 |     | 600 | 2.1                             | 1.8 | 2.4  | 2.0  | 2.5 | 2.4 | 11.2               | 8.0  | 10.0 | 12.2 | 15.1 | 17.0 |
| J W     | 555  | 600 | 610 | 600 | 560 |     | 2.0                             | 2.0 | 3.1  | 3.0  | 2.9 | 2.7 | 12.0               | 13.0 | 16.1 | 19.2 | 20.0 | 22.1 |
| H O     | 580  | 610 | 630 | 605 | 575 | 540 | 2.0                             | 4.0 | 4.1  | 4.8  | 4.2 | 3.3 | 18.1               | 22.0 | 17.3 | 16.4 | 22.7 | 18.0 |

cral times, each time with similar results, the temperature sometimes rising to 102° F. After 'salt loading,' the polyuria was more marked, but still not profound. We have classified this patient as a 'primary thirst' type of diabetes insipidus.

**Salt loading tests.** Results of these tests for C.A. have been described in detail in a previous report (5). Results of the tests in all of the patients are compared with the normal response in table 2. As contrasted with the normal response, the significant findings in all patients were a), a normal range for serum chlorides, b), and inability to concentrate salt in the urine, and c), a further increment in the already increased output of urine per minute.

The results of the influence of low and high salt intake, estrogens, desoxycholesterone acetate, and amidopyrine upon fluid balance in H.O. and J.W. are summarized in figures 1 and 2, and tables 3 and 4. Data for C.A. are contained in a previous report (5) and agree in all particulars with the findings in patient J.W.

**Low salt feeding.** If the diet was changed from one containing 11.3 gm of sodium chloride (average dietary intake) to one containing approximately 3.9 gm of sodium chloride, there was an overall reduction in urinary volume of approximately 30 per cent. The time necessary for maximum effect varied from individual to individual but was usually apparent in from 3 to 7 days (fig. 3).

**High-salt feeding.** In patient H.O., 30 gm of salt was used daily with an increase of approximately 25 per cent in the urinary output, a moderate rise in the specific gravity, and a two-fold increment in the concentration of chloride. J.W. responded to half of this amount of sodium chloride with almost a 30 per cent rise in urinary volume, a very slight, perhaps insignificant, rise in specific gravity, and a 25 per cent elevation in the concentration of chloride.

**$\alpha$  Estradiol dipropionate.** In patient J.W., following the daily use of 10 mg of  $\alpha$  estradiol dipropionate,<sup>2</sup> there was a definite reduction in urinary output, slightly greater than that seen from a regime of low-

salt feeding. This, however, was not in evidence until the 4th day of treatment and did not reach its maximum until the 9th day (fig. 4). Concurrently there was a slight rise in specific gravity, no appreciable effect upon urinary chloride concentration, and a marked positive balance in chloride metabolism with increase in weight.

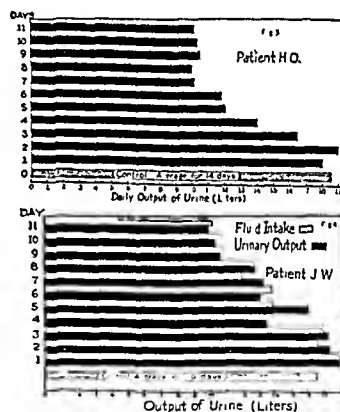


Fig. 3 INFLUENCE OF LOW SALT INTAKE ON URINARY OUTPUT IN DIABETES INSIPIDUS. The diet contained 1.5 gm of Na ( $\approx 3.9$  gm of NaCl). Fig. 4 INFLUENCE OF ESTROGENS ON FLUID INTAKE AND URINARY OUTPUT IN DIABETES INSIPIDUS. Diet contained 4.5 gm of Na (as NaCl  $\approx 11.3$  gm)  $\alpha$  Estradiol dipropionate, 10 mg daily dosage.

In patient H.O., during a 5-day period, the estrogen in daily doses of 10 mg had no appreciable effect upon either the volume of urine or the concentration of the urinary chlorides. There was, however, significant retention of sodium chloride.

The influence of estrogens upon patient C.A. was not studied.

As a result of clearance tests<sup>2</sup> it was shown that the estrogen did not affect glomerular filtration appreciably, but that it did materially increase tubular

<sup>2</sup> We are indebted to Dr. H. Elias for making clearance tests in connection with this and our other work.

TABLE 3. URINARY VOLUME, CONCENTRATION AND CHLORIDES IN DIABETES INSIPIDUS UNDER VARIED CONDITIONS, PATIENT H.O.

| Regime                                   | Highest Specific Gravity | Averaged 24-hour   |                    |             | Urinary Concentration of Cl, % as NaCl | Pody Weight, lb. |
|--|--------------------------|--------------------|--------------------|-------------|--|------------------|
|  |                          | Urinary output, l. | Total Cl (as NaCl) |             |  |                  |
|  |                          |                    | Intake, gm.        | Output, gm. |  |                  |
| Control                                  | 1.005                    | 18.6               | 11.3               | 11.2        | 0.060                                  | 160              |
| Low salt                                 | 1.006                    | 12.9               | 3.9                | 3.8         | 0.029                                  | 161              |
| High salt                                | 1.006                    | 23.3               | 30.1               | 29.8        | 0.127                                  | 164              |
| High salt and amidopyrine <sup>1</sup>   | (a) 1.008                | 18.2               | 30.1               | 36.6        | 0.201                                  | 163              |
|  | (b) 1.008                | 19.1               | 30.1               | 31.9        | 0.166                                  | 163              |
| High salt and pitressin <sup>2</sup> (c) | 1.017                    | 5.1                | 30.1               | 30.4        | 0.596                                  | 162              |
| Average salt and pitressin <sup>2</sup>  | 1.015                    | 1.6                | 11.3               | 11.3        | 0.706                                  | 167              |
| D.C.A. <sup>3</sup>                      | 1.004                    | 18.2               | 11.3               | 11.4        | 0.062                                  | 167              |
| After D.C.A. <sup>4</sup>                | 1.006                    | 17.1               | 11.3               | 15.2        | 0.089                                  | 164              |
| Estrogen <sup>5</sup>                    | 1.006                    | 18.4               | 11.3               | 9.7         | 0.052                                  | 166              |

Each figure represents an average of from 2 to 5 determinations, none of which was made until the treatment indicated had been employed for at least 3 days. Control periods between each 2 test periods of not less than 5 days each were utilized.

<sup>1</sup> 2 gm. daily; (a) 1st and 2nd days; (b), 12th and 14th days.  
<sup>2</sup> Pitressin tannate in oil, 1 cc. daily. (c), 1 determination, 4th day.  
<sup>3</sup> 10 mg. daily.  
<sup>4</sup> First day after desoxycorticosterone acetate discontinued.  
<sup>5</sup>  $\alpha$ -Estradiol dipropionate, 10 mg. daily.

resorption of salt and, in one instance, of water as well. That the dosages used in these studies are not physiologic is evidenced by the fact that, after having received the estrogen for 7 or 8 days, patient J.W., a strong, virile type of mulatto, complained of

TABLE 4. URINARY VOLUME, CONCENTRATION AND CHLORIDES IN DIABETES INSIPIDUS UNDER VARIED CONDITIONS, PATIENT J. W.

| Regime                                  | Highest Specific Gravity | Averaged 24-hour   |                   |             | Urinary Concentration of Cl, % as NaCl | Body Weight, lb. |
|---|--------------------------|--------------------|-------------------|-------------|--|------------------|
|   |                          | Urinary output, l. | Total Cl, as NaCl |             |  |                  |
|   |                          |                    | Intake, gm.       | Output, gm. |  |                  |
| Control                                 | 1.002                    | 16.5               | 11.3              | 11.0        | 0.065                                  | 163.0            |
| Low salt                                | 1.003                    | 11.7               | 3.9               | 4.1         | 0.035                                  | 163.5            |
| High salt                               | 1.004                    | 21.3               | 15.0              | 15.2        | 0.080                                  | 162.5            |
| Estrogen <sup>1</sup>                   | 1.004                    | 10.0               | 11.3              | 7.8         | 0.070                                  | 168.5            |
| High salt and pitressin <sup>2</sup>    | 1.012                    | 5.3                | 30.0              | 28.7        | 0.540                                  | 162.5            |
| Average salt and pitressin <sup>2</sup> | 1.013                    | 2.7                | 13.8              | 14.0        | 0.510                                  | 164.0            |
| High salt and amidopyrine <sup>3</sup>  | 1.009                    | 18.2               | 30.0              | 30.3        | 0.166                                  | 163.0            |
| D.C.A. <sup>4</sup>                     | 1.003                    | 15.4               | 11.3              | 9.8         | 0.063                                  | 167.0            |
| After D.C.A. <sup>5</sup>               | 1.004                    | 14.0               | 11.3              | 17.8        | 0.127                                  | 165.0            |

Each figure represents an average of from 2 to 5 determinations, none of which was made until the treatment indicated had been employed for at least 3 days. Control periods between each two test periods of not less than 5 days each were utilized.

<sup>1</sup>  $\alpha$ -Estradiol dipropionate, 10 mg. daily.  
<sup>2</sup> Pitressin tannate in oil, 1 cc. daily.  
<sup>3</sup> 2 gm. daily.  
<sup>4</sup> 10 mg. daily.  
<sup>5</sup> Second day after desoxycorticosterone acetate discontinued.

diminution in power of erection and in sex desire, associated with which there appeared a sensitiveness of the breasts with slight intensification of the pigmentation and feminization of the secondary mammary areolae.

Desoxycorticosterone acetate. As a result of the daily administration of 10 mg of desoxycorticosterone acetate<sup>1</sup> to patients J W and H O for periods of 4 and 5 days, respectively, there was no alteration of the fluid exchange. However, some retention of sodium chloride occurred, which was rather promptly released in the period following treatment. This was more striking in the case of J W than in that of H O and was thought to be related to the difference in the type of diabetes insipidus present in each instance. Chloride and inulin clearance tests showed that, in the dosages used, desoxycorticosterone acetate caused a marked increase in the tubular resorption of sodium and chloride, which was compensated for as soon as the effect of the drug began to decline.

#### CASE REPORTS

Case 1, C A,<sup>2</sup> a 30 year-old white male, developed polyuria (up to 28,000 cc daily) and polydipsia at the age of 18 shortly after recovering from a post pneumonic encephalitis. At the age of 26 he was given intensive anti syphilitic treatment. During the period of the present observations he was suffering from advanced pulmonary tuberculosis, which eventually resulted fatally.

The anatomical diagnoses made following postmortem examination were: bilateral caseous ulcerative tuberculous of the lungs, to which death was attributed, amyloidosis of the liver, spleen, and kidneys, tuberculous ulceration of the small and large intestines, degeneration of the supraoptic nucleus and of the posterior lobe of the pituitary gland, in association with diabetes insipidus.

Case 2, H O, a white male now 20 years old, has been under observation since the age of 16, at which time he was admitted to the hospital complaining of pain in the lower right quadrant of the abdomen so severe in nature that appendectomy was performed for a relatively normal appendix. During the post operative course, the fluid intake and output averaged approximately 24 liters daily. He stated that polyuria and polydipsia had been present since the age of 2 years. There was an average nocturia of 6 and a diuria of 25 times because of which it had been impossible for him to retain a position of any sort. If he attempted to decrease his intake of water, severe abdominal pain invariably ensued which had led to hospitalization on several occasions.

As to the

He had

He had measles, mumps, chicken pox, and whooping cough in childhood. Tonsillectomy and adenoidectomy were performed at the age of 4. For most of his life he has suffered from generalized headaches recurring periodically every 3 to 4 days and unrelated in any way to food or water intake or to time of day. At times his vision has

been blurred, and he has found that he cannot see things to the side. He has had no attacks of complete blindness, convulsions, unconsciousness, or motor or sensory loss. He has never experienced any olfactory, auditory, gustatory or visual hallucinations.

On physical examination, one observed an undersized individual of unusual appearance. The frontal bosses were prominent, the eyelids were puffy and slanted in a Mongolian like fashion, and the eyeballs were prominent. There was a divergent squint, despite which the interpupillary distance was disproportionately small. There was a short, saddle type nose, the lower jaw protruded slightly, the lips were thick, and labial speech was disturbed. His weight was 147 lb, height, span, and lower measurement, 60, 61, and 30 5 inches, respectively. The distribution of fat pads suggested that of a Frohlich's syndrome, although all other features, such as sex organs, hair distribution, and other secondary sex characteristics were normal. The neck was short, thick, and full. The heart and lungs were negative, the blood pressure was 116 and 70 mm Hg systolic and diastolic, respectively. Rectal examination revealed a prostate of normal size. All reflexes were bilaterally symmetrical and equal, no pathologic reflexes could be elicited.

Since many of the laboratory tests performed in connection with this case have been repeated frequently without material alteration through the years, the results of a few representative analyses follow. The blood Wassermann reaction was negative. Routine urinalysis was negative save for the low specific gravity and the large volume. Blood plasma proteins in percentage were: albumin, 4.1, globulin, 2.1, and fibrinogen, 0.32, total, 6.52. Other blood chemical constituents in mg per cent were: urea nitrogen, 9.0, creatinine, 0.8, sugar, 75, chlorides (as NaCl) 553, rising slightly in response to salt loading tests, but returning to normal within 6 hours, total lipids, 868, free fatty acids, 52, neutral fats, 310, total cholesterol, 202, free cholesterol, 56, esters, as cholesterol oleate, 247, lipid phosphorus, 8.6, and phospholipids, 203. The blood count was normal. The red cells sedimented 2 mm in 15 minutes, and 10 mm in one hour. Blood sugars at hourly intervals following the oral ingestion of 100 gm of glucose were, in mg per cent, 67, 94, 92, 75 and 70 respectively. The spinal fluid was clear, it was under no increase in pressure, showed a total protein of 24 mg per cent with no increase in globulin, chlorides, as NaCl, 692 mg per cent, and colloidal gold curves were unmodified. The basal metabolic rate was -12. The electrocardiographic tracing was normal throughout. The Wassermann reaction was negative.

A gastro intestinal roentgenographic series revealed no pathology. Roentgenograms of the skull showed a sella turcica of relatively small proportions as compared with the size of the cranial cavity, the posterior clinoid processes were unusually thick and erect. The sphenoidal sinus was poorly developed.

On ventriculography and encephalography, no abnormality of the ventricular system could be made out, although the neuro surgeon made a note to the effect that the pia arachnoid was somewhat thickened and, in the absence of pressure signs, interpreted this as the result of an old meningoencephalitis.

<sup>2</sup> Findings in this case have been reported in detail elsewhere (see reference 5).

Periods of tubular vision have alternated with normal vision. Revised Stanford-Binet intelligence tests revealed a mental age of approximately 13 years.

*Comment.* The patient states that there have been spontaneous remissions, lasting as long as several weeks, in the polyuria and polydipsia with a urinary output not exceeding 3,000 cc. daily on some occasions. However, such changes have not been present during hospitalization except following encephalography, after which the output decreased for a few days to about 3,500 cc.

*Final diagnosis.* Diabetes insipidus and mental and physical retardation secondary to an old meningoencephalitis.

*Case 3, J.W.,* a 39-year-old male mulatto, has suffered from polydipsia, polyuria, and pollakiuria for as long as he can remember. He stated that he had been accustomed to pass about 5 gallons of urine every 24 hours, and that continuous water drinking and urgency to urinate had forced him to give up or caused him to be discharged from a number of positions he could otherwise have held without difficulty. He recalled having had severe febrile attacks each fall for 3 successive seasons during childhood. His birth was normal; and teething, walking, and talking were all accomplished at the usual ages. There were no other significant facts in his own past history or in his family history.

Physical examination revealed a well-developed, well-nourished, muscular individual, 71 inches tall and weighing 162 lb. His physical examination was essentially negative. The blood pressure was 132 and 82 mm. Hg systolic and diastolic, respectively. The eyegrounds were normal; all reflexes were normal and no pathological ones were present. Laboratory studies made at or near the time of admission led, with the exception of the urine, to normal findings. The electrocardiogram was normal. Roentgen-ray examinations of the chest, skull, and pelvis revealed no pathologic changes. Repeated routine urine analyses showed nothing abnormal save a specific gravity routinely below 1.003. The blood Wassermann reaction was negative. The blood count showed a hemoglobin of 81 per cent, a red cell count of 4.8 million per cu. mm., a white cell count of 8.4 thousand per cu. mm., and a differential count (in per cent) of polymorphonuclear neutrophils, 72; lymphocytes, 24; and eosinophiles 4. The basal metabolic rate was -6. Blood proteins in per cent were: albumin, 4.34; globulin, 2.91; total, 7.47. Other blood chemical constituents, in mg. per cent, were: urea nitrogen, 10; creatinine, 0.9; sugar, 90; chlorides (as NaCl), 575; sodium, 332.9; potassium, 18.6; total cholesterol, 176; and cholesterol esters, 118.

His course in the hospital was uneventful except for variations in water and salt balance and can best be followed by study of figures 2 and 4, and tables 1, 2 and 4.

*Final diagnosis.* Diabetes insipidus of undetermined etiology, possibly familial in type.

## DISCUSSION

*Types of diabetes insipidus.* Perhaps by definition we should confine the use of the term diabetes insipidus to that type of polyuria and polydipsia associated with a depressed or destroyed function of the supraoptico-hypophyseal tract and the posterior pituitary, as a result of which posterior pituitary secretion is lessened or stopped, and the kidney loses much of its regulatory power over the resorption of water from the tubules. With such a definition, the primacy of the polyuria among the symptoms of the disease cannot be denied, and has been amply proven by Ranson and his associates (1), who have critically reviewed the literature.

The type of polyuria seen in one of the patients (H.O.) described above would have no place in such a definition of the disease. Yet, except for water-deprivation tests, polyuria in this case reacted similarly to that of the patients with the classical syndrome. The prompt response to posterior pituitary substance would appear to preclude the condition being of the hysterical type of polydipsia and polyuria. That such responses were not psychic was demonstrated by the fact that no other treatment gave him as much relief or caused such good concentration of the urine as did the posterior pituitary substance. Moreover, saline injections were given in the place of the pitressin, with the same technique and psychological management. Despite this fact, urinary volume rose, and the specific gravity and urinary concentration of chlorides decreased.

As can be seen from his history, this patient had periods of relative freedom from the condition, rather than the permanent polyuria of the more classical type. Similar cases have been previously described in human beings (6) and in dogs (7). Experimentally, the existence of a thirst-primacy type of diabetes insipidus has always been open to question (1). While Curtis' (8) view that all diabetes insipidus can be looked upon as a 'hypothalamic thirst phenomenon' is untenable, it does, however, appear that not one but a number of factors influence the character and clinical behavior of the syndrome known as diabetes insipidus. We should not, therefore, overlook disturbances in water balance which may fail to conform to a single rigid pattern (9). This is particularly worthy of emphasis at a time when thyroid substance (1, 10), pancreatic (11), adrenal, and renal extracts, vitamins (12), and other materials of equally diverse origin have been shown to exert an effect upon fluid exchange within the body.

*Influence of sodium chloride.* Urinary output could be lowered or raised at will in all 3 of our patients by a reduction or increase, respectively, in the amount of salt ingested. This variation was directly propor-

tional to the amount of salt in the diet, but was not of straight line magnitude. In response to these changes, sodium and chloride balance was maintained not only by an increase or decrease in the quantity of the urine, but also by a variation in the amount of tubular reabsorption. It would appear that salt itself is capable of increasing the ability of the renal tubules to resorb water. It must be remembered that no case of human diabetes insipidus has ever been recorded in which this function was entirely lost (1, 13, 14). For this reason, it may be possible that salt exerts its effect not upon the kidney tubule directly but upon the remaining function of the supra-optico hypophyseal system through which the anti-diuretic hormone is produced. Both Peters (15) and Fisher and his associates (1) emphasize the primary effect of this hormone on the reabsorption of water from the kidney tubule and stress the fact that this action is out of all proportion to its influence upon the excretion of solutes. On the other hand, in our patient C A, no trace of intact fibers within the supra-optico hypophyseal tract could be found, and atrophy of the cells of the posterior pituitary was striking. Nevertheless, the power to produce some concentration of the urine was not entirely lost. These observations suggest a certain degree of autonomous action on the part of the kidney itself.

From the present studies, we are justified only in emphasizing the stimulating effect of salt upon the tubular resorptive power of the kidney, for the higher the concentration of salt, the better the tubule succeeded in its effort to resorb water.

**Influence of estrogen.** In connection with our observations, it would appear that the human being with diabetes insipidus responds to large dosages of an estrogen in much the same manner as does a normal person. Thorn (16, 17) has noted a retention of body fluid and electrolyte in the normal individual under the influence of follicular hormone. Some workers do not agree with this conclusion, but the differences of opinion on this subject may be related to the fact, emphasized by Thorn himself, that the action is temporary and cannot be maintained even by the continued administration of the hormone. During the period of observation in the present studies (up to 11 days), the patients remained in a phase of positive sodium and chloride balance. Because of the prolonged action of the  $\alpha$  estradiol dipropionate the reversion to normal was gradual, and could not be closely followed by the methods at hand. In view of the unpleasant reaction in one patient and the failure to reduce urinary volume appreciably even with large doses, the hormone possesses little if any therapeutic value in a disease like diabetes insipidus. However, its

positive influence upon water and salt balance has been well demonstrated in our cases.

Such a statement justifies more than passing comment, as the rôle of the estrogens in disturbing the water and salt distribution in menstruating women has been as frequently denied as confirmed. This is the first study of the effects of the estrogens in a disease in which variations in electrolyte and fluid equilibrium are unusually easy to follow. It would appear that many authorities have unnecessarily minimized the ability of follicular hormone to create a positive balance in the body for both water and salt.

**Influence of desoxycorticosterone acetate.** In view of the now well known ability of desoxycorticosterone acetate to produce a syndrome not unlike that of diabetes insipidus (7, 18-23) it was rather surprising to find in the literature no report of the study of the hypothalamic region in such animals. Almost equally strange was the absence of any investigation of the influence of desoxycorticosterone acetate upon the already-established diabetes insipidus of lower animals and man.

The frequently observed diuresis associated with the administration of large doses of desoxycorticosterone acetate and a high salt intake in laboratory animals has been studied critically by Mulinos and his associates (18) in an effort to establish a relationship between it and diabetes insipidus. In the experience of these workers, salt-loading and restriction, and water-loading and deprivation tests have resulted in changes that are comparable in every respect to the alterations in water and salt metabolism which are seen in animals with diabetes insipidus. Their work suggests that the syndrome of diabetes insipidus may arise either from a specific destructive lesion of the hypothalamic and posterior hypophyseal regions, or from an overactivity of certain functions of the adrenal cortex. In further proof of the correctness of this view stands the evidence that adrenalectomy has improved the diuresis of animals with diabetes insipidus (24-27).

On the basis of these facts, one would have expected the use of desoxycorticosterone acetate in our patients to be accompanied by a further increase in urinary volume in an effort to eliminate the retained sodium. This was not the case, despite the fact that the retention of sodium as a result of administration of desoxycorticosterone acetate was easily demonstrated, and its rapid elimination observed as soon as the drug action was spent. Our periods of observation may have been too short for development of the diabetes insipidus like effects, for it seems to be well established that, during the earliest days of administration to dogs, a retention of chloride without appreciable diuresis may occur (18). Moreover, the dose of



desoxycorticosterone acetate may have been too small to elicit the polyuric and saline diuretic actions, but it seemed to be the largest dose compatible with safety in the human being on the basis of previous studies in patients with Addison's disease (28).

It may be argued that the increased excretion of chloride and sodium obtained after discontinuing desoxycorticosterone acetate in our patients was due to the saline diuresis it may produce. On the contrary, this increase in urinary chloride was associated with no change or, indeed, with a slight decrease rather than an increase, in urinary volume.

The diuresis of diabetes insipidus and that of desoxycorticosterone acetate intoxication seem to differ in yet another way. With the diuresis of desoxycorticosterone acetate, the blood serum sodium usually rises, whereas in diabetes insipidus it is apparently never elevated. The significance of this difference is not apparent and may be a matter of degree only, or, on the other hand, a function of time. Most of the observations on serum sodium levels in diabetes insipidus have been made after the disease had been present for considerable periods of time, i.e., after the body had had an opportunity to adjust sodium and chloride balance by the excretion of large quantities of urine of a low specific gravity; whereas in the majority of the studies of desoxycorticosterone acetate intoxication, the interval of observation has been short and the long-continued influence of the drug on electrolyte balance has received little or no attention. It is our experience that the high levels of blood sodium seen in cases of Addison's disease under treatment with high dosage of desoxycorticosterone acetate give way sooner or later to more normal or entirely normal values, even if the intake of sodium is varied. This would suggest that, if sufficient time is allowed, the chloride balance in desoxycorticosterone acetate poisoning may behave in a manner not unlike that seen in the animal with diabetes insipidus.

#### SUMMARY

1. The clinical findings in three cases of diabetes insipidus are summarized.
2. Changes in the volume, concentration, and sodium and chloride content of the urine under a variety of influences, including low and high salt intake, posterior pituitary substance, amidopyrine, follicular hormone, and desoxycorticosterone acetate, have been detailed.
3. Low salt intake decreases the urinary volume and lowers the chloride concentration. High salt intake increases the volume as well as the concentration.
4. In two patients, water deprivation was attended by a relative failure to check urinary output, whereas in the third patient, it was reduced nearly to the level of water intake.

5. Estrogen caused a retention of sodium and chloride in all patients and an appreciable reduction in the volume of urine, but made no change in its specific gravity.

6. Desoxycorticosterone acetate produced a positive sodium and chloride balance but did not materially influence the volume of the urine in any of the three patients. The retention of salt was accompanied by a rapid gain in weight and was followed temporarily by a marked negative balance of sodium and chloride.

7. Amidopyrine in the dosages used raised the specific gravity and the chloride concentration of the urine, but had little or no influence upon the total chloride excretion.

8. Posterior pituitary substance exerted its characteristic anti-diuretic effects in each patient. This was true irrespective of whether each was receiving a high, average, or low salt intake, although the urinary volume was least whenever a low sodium chloride intake was employed.

#### CONCLUSIONS

The primary disturbance following a deficiency in the secretion of the posterior lobe of the pituitary gland occurs in the kidney tubules and appears to be either *a*), a failure in the preferential re-absorption of water, or *b*), a too-avid resorption of salt, or *c*), both.

The water-resorptive power of the tubule is decreased by low salt intake, and increased by high salt intake, amidopyrine, posterior pituitary substances, and estrogens.

The salt-resorptive power of the tubule is increased by estrogens and desoxycorticosterone acetate, and decreased temporarily by desoxycorticosterone acetate in the phase following treatment.

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# Use of Testosterone Propionate and Estrogenic Substance in Treatment of Essential Hypertension, Angina Pectoris and Peripheral Vascular Disease

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THE EFFECT of the sex hormones in cardiovascular disease has been the subject of relatively few clinical investigations. In recent medical literature, however, several reports have been published indicating that these substances may find a useful place in the management of certain vascular disorders. In 1939, Edwards, Hamilton and Duntley (1) observed objective and subjective improvement in 7 male patients with organic peripheral vascular disease following treatment with testosterone propionate. All patients presented evidence of major arterial involvement with loss of the popliteal, femoral, and in one case, the iliac pulsations. In 1940, I presented data (2), indicating that the sex hormones gave promise of being effective in the treatment of vascular insufficiency of the coronary, cerebral, and peripheral circulatory systems. Such salutary results were manifested among patients with angina pectoris in an increase of emotional and exercise tolerance, a decrease in the severity of pain, and a general increase in strength. Improvement of the peripheral circulation in patients with occlusive vascular disease was indicated by a return of normal color and temperature, decrease or complete cessation of pain, healing of gangrenous ulcers, increase in exercise tolerance, and an increase in the volume of the peripheral pulse. Subjective evidence of improved cerebral circulation occurred frequently in patients exhibiting clinical syndromes suggesting cerebral circulatory insufficiency.

Since the publication of this study at least three other authors have reported favorable results in the treatment of coronary insufficiency with male hormone. Bonnell, Pritchett, and Rarden (3) observed significant clinical improvement in 22 of 23 patients with angina pectoris and coronary artery disease. Lesser (4) reported excellent results in all patients of a group of 20 men and 4 women exhibiting characteristic angina pectoris. Control patients treated with plain sesame oil did not improve, although subse-

quently these individuals showed a favorable response to male hormone therapy. The majority of the patients in Lesser's series showed some lowering of the blood pressure during the period of treatment with testosterone propionate. Hamm (5) has recently reported a favorable therapeutic response to male hormone therapy in 7 male patients with unquestionable angina pectoris.

Among European investigators, Steinach and his co-workers (6) observed a fall in systolic blood pressure in 31 of 49 hypertensive individuals treated with androgenic substance. Arndt (7) found testosterone propionate to be therapeutically effective in the treatment of 5 male patients with peripheral vascular disease and 3 male patients with angina pectoris. Greene (8), treating 21 male patients for prostatic hypertrophy with testosterone, observed no significant change in the blood pressure levels of hypertensive individuals in his series. It is not clear to what extent prostatic obstruction and consequent urinary retention were etiologically concerned in the production of hypertension in these patients.

## CLINICAL MATERIAL AND METHOD OF STUDY

A clinical study of the effect of the sex hormones in cardiovascular disease has been made in the cardiac clinic of the Beaumont Medical Dispensary since January, 1939. Although this study was originally initiated to determine the effect of these substances in essential hypertension, a few patients with angina pectoris and organic vascular disease of the extremities with and without associated hypertension were subsequently included in this investigation. In the course of this study 82 individuals were treated with androgenic and estrogenic substance. Among these patients 56 exhibited primary hypertension; 12 had angina pectoris, and 14 showed physical and symptomatic evidence of organic peripheral vascular disease.

*General limitations.* In all groups, treatment was limited to ambulatory individuals who were not in

congestive heart failure and who had not suffered a recent coronary occlusion. Sex hormone therapy was further confined to patients who were not obviously ill from any cause other than cardiovascular disease. During the period of treatment with androgenic and estrogenic substances all other general and specific therapeutic measures were suspended. Female patients were treated with standard preparations of estrogenic substance<sup>1</sup> by intramuscular injection. Mixed estrogens and estrone were given in 10,000 I.U. doses, estradiol dipropionate was given in dosages of 0.2 mg. The schedule usually followed was as follows: 4 injections in the first week, 3 injections weekly for the next 4 weeks, 2 injections weekly for the succeeding 4 weeks, and thereafter one injection weekly for 4 more weeks.

Male patients were treated with testosterone propionate<sup>2</sup> by intramuscular injection. In the 1st week 4 doses of 25 mg. each, 2nd week, 3 injections of 25 mg. each, 3rd and 4th weeks, 10 mg. 3 times weekly, 5th through 8th week, 10 mg. twice weekly, 9th through 12th week, 10 mg. weekly.

**Hypertension.** For the purpose of this study individuals were selected who, on two or more visits to the clinic, presented a consistent elevation of both systolic and diastolic blood pressure levels, and in whom a definite cause for the hypertension could not be ascertained. Hence, patients were excluded who had definite renal lesions, urinary tract obstruction, aortic regurgitation, or any condition definitely known to produce hypertension. Associated arteriosclerosis was not considered an etiologic factor although hypertensive individuals with angina pectoris and/or organic peripheral vascular disease were not included in this group.

**Angina pectoris.** A diagnosis of angina pectoris was acceptable only when, among other manifestations, a constant, severe, substernal discomfort was routinely precipitated by a given amount of work, and routinely relieved by rest.

**Peripheral vascular disease.** All patients accepted for study in this group showed loss of the dorsalis pedis, posterior tibial, popliteal, femoral, or iliac pulsation associated with definite signs of impaired peripheral circulation.

#### Blood Pressure Studies

An analysis of the data in tables 1 and 2 indicates that 81 per cent of the 56 patients showed some lowering of the blood pressure during treatment with the sex hormones. In 33 per cent of all patients the blood pressure showed a significant fall but did not

approach a normal level. In 28 per cent the blood pressure returned to, or near, normal figures. The available data on the blood pressure after the cessation of sex hormone therapy indicates that more often than not blood pressures returned to previously high levels, although some lowering of the blood pressure was sustained in a few patients for as long as 6 months after suspension of treatment.

The blood pressure level was not usually affected in patients who demonstrated the higher grades of hypertension associated with symptoms and physical evidence indicating advanced vascular damage. A few patients were exceptions to this observation and the occurrence of transient episodes of marked elevation of blood pressure in this group was definitely reduced. Patients showing a moderate elevation of blood pressure along with symptoms and objective evidence of mild to moderate vascular damage, generally responded more favorably, but the results in this group also were varied. In some instances a return of the blood pressure to, or near, a normal level was affected while in other individuals the blood pressure was not materially changed. There was a rather consistent fall of systolic pressure in those individuals who presented the so-called 'benign' type of hypertension with a high systolic pressure and relatively little elevation of the diastolic pressure. Most of these patients had an associated generalized arteriosclerosis and it is possible that the hypertension in these cases is not etiologically akin to the hypertension among the other patients in this series. Patients presenting evidence of vasospastic or mild hypertension, without vascular damage, routinely responded favorably, a return of the blood pressure to normal being effected in all patients in this group.

Among those patients who demonstrated a fall in blood pressure during sex hormone therapy, it generally appeared that the effect on the blood pressure was inversely proportional to the degree of hypertension, and to the apparent extent of vascular damage. The group of patients who failed to show a significant response includes individuals with no apparent vascular damage as well as some whose symptoms and physical findings denoted widespread structural changes. In other words, when a hypertensive subject was not affected by sex hormone therapy this failure could not always be correlated with the degree of hypertension nor the extent of structural vascular changes.

#### CASE REPORTS

C. S., a male negro, age 58, complained of severe headaches, dizziness, loss of strength and subjective nervousness. These symptoms had progressively developed during the preceding 6 months. Blood count, Wassermann reaction, basal metabolic rate, and electrocardiographic tracing were within normal limits. The results of urine

<sup>1</sup> The estrogens employed were estradiol dipropionate (Di Ovovion) and estrone (Ovovion).  
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 Detrol.

<sup>2</sup> Testosterone propionate (Perandren) was supplied for this study by Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE ON BLOOD PRESSURE IN MALE PATIENTS WITH ESSENTIAL HYPERTENSION

| Case No. | Age, yr. | Race | Treatment and Observation Before Sex Hormone Therapy |            |                               | Effect of Sex Hormone Therapy on Blood Pressure |                          | Subsequent Observation                      |                        |
|----------|----------|------|--|------------|-------------------------------|---|--------------------------|---|------------------------|
|          |          |      | Time   | Treat-ment | Blood pres-sure range, mm. Hg | Beginning of treatment, mm. Hg                  | End of treatment, mm. Hg | Time after sex hormone therapy discontinued | Blood pressure, mm. Hg |
| 1        | 56       | W    | 1 yr.  | Yes        | $\frac{170-165}{110-100}$     | $\frac{165}{100}$                               | $\frac{120}{85}$         | 5 months                                    | $\frac{130}{90}$       |
| 2        | 43       | W    | 1 mo.  | No         | $\frac{150}{90}$              | $\frac{150}{90}$                                | $\frac{120}{80}$         | 2 months                                    | $\frac{125}{85}$       |
| 3        | 50       | N    | 2 mo.  | Yes        | $\frac{190-170}{110}$         | $\frac{170}{110}$                               | $\frac{140}{90}$         |   |                        |
| 4        | 55       | W    | 1 mo.  | No         | $\frac{170}{110}$             | $\frac{170}{110}$                               | $\frac{155}{90}$         | 2 months                                    | $\frac{160}{100}$      |
| 5        | 67       | N    | 7 mo.  | Yes        | $\frac{190}{110}$             | $\frac{170}{90}$                                | $\frac{135}{85}$         |   |                        |
| 6        | 58       | N    | 3 mo.  | Yes        | $\frac{200-195}{115-105}$     | $\frac{195}{105}$                               | $\frac{140}{90}$         | 7 months                                    | $\frac{180}{100}$      |
| 7        | 60       | N    | 1 mo.  | No         | $\frac{170}{100}$             | $\frac{170}{100}$                               | $\frac{160}{105}$        | 3 months                                    | $\frac{160}{100}$      |
| 8        | 56       | N    | 1.5 yr.  | Yes        | $\frac{200-210}{130}$         | $\frac{210}{130}$                               | $\frac{200}{135}$        | 1 month                                     | $\frac{210}{135}$      |
| 9        | 62       | N    | 1 yr.  | Yes        | $\frac{160-165}{90-100}$      | $\frac{165}{100}$                               | $\frac{160}{90}$         | 4 months                                    | $\frac{160}{80}$       |
| 10       | 46       | N    | 1 mo.  | No         | $\frac{170}{105}$             | $\frac{170}{105}$                               | $\frac{140}{90}$         |   |                        |
| 11       | 52       | W    | 1.5 yr.  | Yes        | $\frac{160-180}{90-110}$      | $\frac{170}{100}$                               | $\frac{138}{88}$         | 4 months                                    | $\frac{145}{90}$       |
| 12       | 46       | W    | 2 yr.  | Yes        | $\frac{140-160}{90-115}$      | $\frac{160}{115}$                               | $\frac{140}{90}$         | 3 months                                    | $\frac{140}{100}$      |
| 13       | 26       | W    | 6 mo.  | Yes        | $\frac{160-180}{100-110}$     | $\frac{170}{100}$                               | $\frac{150}{90}$         | 4 months                                    | $\frac{160}{90}$       |
| 14       | 80       | W    | 6 mo.  | No         | $\frac{170-180}{90-100}$      | $\frac{180}{100}$                               | $\frac{140}{80}$         | 3 months                                    | $\frac{140}{80}$       |
| 15       | 60       | W    | 1 mo.  | No         | $\frac{170-180}{90-110}$      | $\frac{170}{90}$                                | $\frac{150}{80}$         | 6 months                                    | $\frac{170}{100}$      |
| 16       | 46       | W    | 1 mo.  | Yes        | $\frac{200-230}{120-130}$     | $\frac{200}{130}$                               | $\frac{170}{120}$        | 1 month                                     | $\frac{170}{120}$      |
| 17       | 43       | W    | 1 mo.  | No         | $\frac{160-170}{110-120}$     | $\frac{160}{110}$                               | $\frac{170}{120}$        | 2 months                                    | $\frac{170}{120}$      |
| 18       | 70       | W    | 3 mo.  | Yes        | $\frac{170-180}{100-110}$     | $\frac{170}{110}$                               | $\frac{150}{90}$         | 2 months                                    | $\frac{170}{100}$      |
| 19       | 56       | W    | 2 yr.  | Yes        | $\frac{200-240}{100-140}$     | $\frac{230}{130}$                               | $\frac{230}{130}$        |   |                        |
| 20       | 60       | W    | 1 mo.  | Yes        | $\frac{190-210}{120-130}$     | $\frac{190}{130}$                               | $\frac{190}{120}$        | 2 months                                    | $\frac{200}{130}$      |
| 21       | 70       | W    | 1 mo.  | No         | $\frac{170}{100}$             | $\frac{170}{100}$                               | $\frac{150}{90}$         |   |                        |
| 22       | 70       | W    | 2 wk.  | No         | $\frac{170}{100}$             | $\frac{170}{100}$                               | $\frac{155}{95}$         |   |                        |

TABLE 1—Continued

| Case No | Age, yr | Race | Treatment and Observation Before Sex Hormone Therapy |           |                             | Effect of Sex Hormone Therapy on Blood Pressure |                         | Subsequent Observation                      |                       |
|---------|---------|------|--|-----------|-----------------------------|---|-------------------------|---|-----------------------|
|         |         |      | Time   | Treatment | Blood pressure range, mm Hg | Beginning of treatment, mm Hg                   | End of treatment, mm Hg | Time after sex hormone therapy discontinued | Blood pressure, mm Hg |
| 23      | 42      | W    | 5 mo   | Yes       | $\frac{210-180}{120-110}$   | $\frac{182}{110}$                               | $\frac{180}{110}$       | 3 months                                    | $\frac{200}{115}$     |
| 24      | 53      | W    | 2 mo   | Yes       | $\frac{200-180}{120-115}$   | $\frac{182}{115}$                               | $\frac{150}{100}$       | 6 months                                    | $\frac{170}{110}$     |
| 25      | 68      | N    | 3 mo   | Yes       | $\frac{260-240}{140-130}$   | $\frac{240}{130}$                               | $\frac{200}{110}$       |   |                       |
| 26      | 38      | N    | 1 wk   | No        | $\frac{200-192}{110-105}$   | $\frac{192}{105}$                               | $\frac{160}{92}$        |   |                       |
| 27      | 47      | W    | 2 wk   | No        | $\frac{180-170}{110}$       | $\frac{170}{110}$                               | $\frac{138}{92}$        | 3 months                                    | $\frac{150}{100}$     |
| 28      | 51      | W    | 6 mo   | Yes       | $\frac{220-210}{130-140}$   | $\frac{210}{140}$                               | $\frac{192}{120}$       | 3 months                                    | $\frac{200}{130}$     |
| 29      | 43      | W    | 1 wk   | No        | $\frac{200}{110}$           | $\frac{200}{110}$                               | $\frac{160}{92}$        |   |                       |
| 30      | 51      | N    | 2 mo   | Yes       | $\frac{170-150}{110-95}$    | $\frac{160}{105}$                               | $\frac{135}{85}$        |   |                       |

analysis were negative, specific gravity was 1.022. Roentgenogram of the heart and great vessels revealed slight widening and tortuosity of the aorta and early left ventricular enlargement. Findings on concentration and dilution tests of renal function were normal. The peripheral arteries showed diffuse thickening, grade I. The blood pressure was 200 mm Hg, systolic and 115 diastolic. Treatment for the next 3 months consisted of a), partial rest, b) maintenance diet, relatively low in fat content, c), aminophyllin 3 grains, 3 times a day, and d), small, regular doses of phenobarbital. At the end of this time he felt somewhat better but still had occasional headaches and dizziness. The blood pressure was 195 mm Hg, systolic and 105, diastolic. All other treatment was suspended and testosterone propionate by intramuscular injection was begun. A placebo was substituted for the phenobarbital. Blood pressure readings progressively decreased and in the 8th week the blood pressure was 140 mm Hg, systolic and 90 diastolic. He volunteered the information that he felt stronger and generally better than he had in 10 years. Attacks of headache and dizziness stopped after the 3rd week of androgenic therapy. Seven months after the cessation of treatment he returned to the clinic complaining of a recurrence of headaches, the blood pressure was 180 mm Hg, systolic and 100 diastolic.

N S, a male, white, age 42, complained of attacks of pounding in the chest, irritability and roaring in the head. Past medical history was insignificant except for one attack of pyelitis. The blood pressure was 210 mm Hg, systolic and 120, diastolic, the pulse was rapid with a rate of 100. Peripheral arteries and eye grounds were normal. The urine was normal with a specific gravity of

1.019, renal function was normal as measured by concentration and dilution tests. Retrograde pyelograms revealed no evidence of renal or ureteral disease. The electrocardiographic curves were within normal limits and a roentgenogram of the thorax was considered to be normal. The basal metabolic rate was -2 per cent.

Theocaine, 15 grains, 3 times a day, along with small doses of phenobarbital, was prescribed and 10 weeks later the nervous symptoms had improved, although he still complained of palpitation, fullness, and roaring in the head. The blood pressure was 190 mm Hg, systolic and 110, diastolic. The theocaine was replaced by potassium thiocyanate administered in sufficient dosage to maintain a blood level between 8 and 12 mg per cent. Eight weeks later he complained of dizziness, nausea, weakness, and considerable subjective nervousness. The blood pressure was 180 mm Hg, systolic and 110, diastolic, the blood thiocyanate was 11 mg per cent. All other therapy was discontinued and treatment with male hormone begun. At the end of another 10 weeks he was extremely pleased with his condition, stating that the disagreeable sensations in his head and chest had ceased to occur, and that all subjective nervousness had disappeared. The blood pressure was 180 mm Hg, systolic and 110, diastolic.

#### Effect on Cerebral Circulation

Evidence in the form of subjective improvement has accumulated in the process of this study suggesting that sex hormones may improve cerebral circulation in some hypertensive individuals. Sixteen patients complained of minor symptoms of probable cerebral origin such as headaches, severe headache

TABLE 2. EFFECT OF ESTROGENIC SUBSTANCE ON BLOOD PRESSURE IN FEMALE PATIENTS WITH ESSENTIAL HYPERTENSION

| Case No.               | Age, yr | Race | Treatment and Observation Before Sex Hormone Therapy |            |                              | Effect of Sex Hormone Therapy on Blood Pressure |                         | Subsequent Observation                      |                        |
|------------------------|---------|------|--|------------|------------------------------|---|-------------------------|---|------------------------|
|                        |         |      | Time   | Treat-ment | Blood pressure range, mm. Hg | Beginning of treatment, mm. Hg                  | End of treatment, mm Hg | Time after sex hormone therapy discontinued | Blood pressure, mm. Hg |
| Estradiol dipropionate |         |      |  |            |                              |   |                         |   |                        |
| 1                      | 44      | W    | 2 yr.  | Yes        | $\frac{230-270}{120-140}$    | $\frac{230}{130}$                               | $\frac{240}{130}$       | Still being treated                         |                        |
| 2                      | 62      | N    | 1 mo.  | No         | $\frac{170-180}{95-110}$     | $\frac{165}{100}$                               | $\frac{135}{85}$        | 6 months                                    | $\frac{145}{90}$       |
| 3                      | 63      | W    | 6 mo.  | Yes        | $\frac{160-170}{90-100}$     | $\frac{170}{100}$                               | $\frac{140}{90}$        | 3 months                                    | $\frac{150}{90}$       |
| 4                      | 58      | W    | 1 yr.  | Yes        | $\frac{170-180}{90-100}$     | $\frac{170}{90}$                                | $\frac{150}{80}$        | 3 months                                    | $\frac{150}{80}$       |
| 5                      | 50      | W    | 2 mo.  | Yes        | $\frac{160}{90}$             | $\frac{160}{90}$                                | $\frac{135}{84}$        | 4 months                                    | $\frac{140}{90}$       |
| 6                      | 46      | W    | 1 wk.  | No         | $\frac{220}{140}$            | $\frac{210}{130}$                               | $\frac{190}{110}$       |   |                        |
| 7                      | 47      | W    | 2 mo.  | Yes        | $\frac{160-170}{100-110}$    | $\frac{160}{100}$                               | $\frac{130}{80}$        | 2 months                                    | $\frac{130}{80}$       |
| 8                      | 55      | W    | 2 mo.  | Yes        | $\frac{180-190}{110-100}$    | $\frac{180}{100}$                               | $\frac{145}{85}$        | 2 months                                    | $\frac{150}{90}$       |
| 9                      | 37      | N    | 6 mo.  | Yes        | $\frac{170-260}{110-140}$    | $\frac{180}{115}$                               | $\frac{180}{115}$       | Still being treated                         |                        |
| 10                     | 46      | N    | 1 mo.  | No         | $\frac{170}{110}$            | $\frac{170}{110}$                               | $\frac{148}{100}$       |   |                        |
| 11                     | 50      | N    | 1 wk.  | No         | $\frac{300}{170}$            | $\frac{300}{170}$                               | $\frac{260}{155}$       | Still being treated                         |                        |
| 12                     | 60      | W    | 2 yr.  | Yes        | $\frac{200-210}{100-110}$    | $\frac{205}{110}$                               | $\frac{165}{85}$        | Still being treated                         |                        |
| Mixed estrogens        |         |      |  |            |                              |   |                         |   |                        |
| 13                     | 55      | N    | 1 yr.  | Yes        | $\frac{150-160}{90-100}$     | $\frac{150}{90}$                                | $\frac{110}{70}$        | 8 months                                    | $\frac{160}{90}$       |
| 14                     | 60      | N    | 1.5 yr.  | Yes        | $\frac{160-210}{100-130}$    | $\frac{160}{110}$                               | $\frac{145}{110}$       |   |                        |
| 15                     | 50      | N    | 1 mo.  | No         | $\frac{190}{115}$            | $\frac{190}{115}$                               | $\frac{145}{100}$       | 2 months                                    | $\frac{160}{100}$      |
| 16                     | 30      | N    | 6 mo.  | Yes        | $\frac{140-150}{90-110}$     | $\frac{150}{110}$                               | $\frac{120}{80}$        | 2 months                                    | $\frac{135}{100}$      |
| 17                     | 48      | N    | 6 mo.  | Yes        | $\frac{160-190}{90-100}$     | $\frac{180}{100}$                               | $\frac{170}{100}$       |   |                        |
| 18                     | 42      | N    | 3 yr.  | Yes        | $\frac{200-230}{100-140}$    | $\frac{210}{140}$                               | $\frac{210}{140}$       | Still being treated                         |                        |
| 19                     | 41      | N    | 2 yr.  | Yes        | $\frac{170-190}{115-120}$    | $\frac{170}{115}$                               | $\frac{150}{100}$       |   |                        |
| 20                     | 62      | W    | 6 mo.  | Yes        | $\frac{210-250}{110-140}$    | $\frac{210}{120}$                               | $\frac{165}{90}$        | 1 month                                     | $\frac{180}{100}$      |

TABLE 2—Continued

| Case No | Age yr | Race | Treatment and Observation Before Sex Hormone Therapy |           |                             | Effect of Sex Hormone Therapy on Blood Pressure |                        | Subsequent Observation                      |                       |
|---------|--------|------|--|-----------|-----------------------------|---|------------------------|---|-----------------------|
|         |        |      | Time   | Treatment | Blood pressure range, mm Hg | Beginning of treatment mm Hg                    | End of treatment mm Hg | Time after sex hormone therapy discontinued | Blood pressure, mm Hg |
| 21      | 52     | W    | 6 mo   | Yes       | $\frac{165-180}{95-100}$    | $\frac{170}{90}$                                | $\frac{150}{85}$       | 1 month                                     | $\frac{150}{85}$      |
| 22      |        | N    | 1 yr   | Yes       | $\frac{220-230}{110-140}$   | $\frac{210}{120}$                               | $\frac{210}{120}$      | 2 months                                    | $\frac{210}{120}$     |

## Estrone

|    |    |   |      |     |                          |                   |                   |          |                   |
|----|----|---|------|-----|--------------------------|-------------------|-------------------|----------|-------------------|
| 23 | 46 | W | 1 yr | Yes | $\frac{180-190}{100-90}$ | $\frac{170}{90}$  | $\frac{150}{90}$  | 2 months | $\frac{150}{90}$  |
| 24 | 60 | W | 1 wk | No  | $\frac{210-200}{110}$    | $\frac{200}{100}$ | $\frac{145}{90}$  | 3 months | $\frac{180}{100}$ |
| 25 | 51 | W | 3 mo | Yes | $\frac{160-170}{110}$    | $\frac{160}{110}$ | $\frac{160}{100}$ | 4 months | $\frac{160}{100}$ |
| 26 | 64 | W | 1 wk | No  | $\frac{180}{120}$        | $\frac{180}{120}$ | $\frac{155}{100}$ |          |                   |

associated with nausea, dizziness, blurring of vision, irritability, subjective nervousness, insomnia, and sensations of fullness and heaviness in the head. Twelve patients in this group obtained symptomatic relief, while 4 were not improved. Six individuals exhibited the more severe cerebral phenomena associated with transient episodes of marked blood pressure elevation (hypertensive encephalopathy), the severity and frequency of such attacks were definitely reduced in 4 individuals while the other 2 were not benefited.

The effect of the sex hormones on the attitude, disposition and mental capacity in some individuals suggests improved cerebral circulation. The return of self-confidence and courage, increase in mental acuity and mental capacity, return of emotional stability and the evolution of a general sensation of well being have been common observations in this series of patients. Such a response is not unusual in the manifestly hypogonadal individual as a result of replacement therapy. Hence, these results cannot be properly accredited to improvement in cerebral circulation. Improvement of cerebral circulation, however, may be the mechanism by which this result is achieved with replacement therapy in hypogonadism.

Patients presenting evidence of definite brain tissue necrosis usually showed no improvement other than that which might have been expected to occur under any other reasonable method of treatment. Four male patients have had cerebral vascular accidents while being treated with male hormone. One died immediately, the other 3 lived and treatment

with male hormone was continued. Progress in these 3 did not appear to be influenced in any way by male hormone therapy.

## CASE REPORTS

C B, a female negro, age 37, complained of recurrent attacks of severe headache accompanied by nausea and vertigo, and followed by spells of unconsciousness. The blood pressure was 210 mm Hg systolic and 130, diastolic, the peripheral arteries showed thickening and sclerosis, grade II Retinal arterioles showed evidence of high grade sclerosis and one area in the left eye ground had been the site of a previous hemorrhage. Roentgenograms of the skull showed no abnormality. The spinal fluid was normal except for a slight increase in pressure. The urine showed a trace of albumen and had a specific gravity of 1.028. Intravenous pyelograms revealed nothing abnormal. Other laboratory findings were within normal limits. During the next 6 weeks, while the patient was taking a xanthine preparation along with phenobarbital and potassium iodide, she had 6 severe attacks such as described above. One of these occurred while she was in the clinic and the blood pressure during the episode was 280 mm Hg systolic, 140 diastolic. The xanthine drug was discontinued and estradiol dipropionate was substituted. In the following month she had two more attacks, in the succeeding two months she experienced only one and it was milder than previous attacks. Two months later she stated that other than an occasional severe headache she had been quite well. The blood pressure was 170 mm Hg systolic and 115, diastolic.

J S W, a white male age 57, complained of loss of strength, extreme subjective nervousness, intense headache and shortness of breath on unusual exertion. He also complained that he was unable to carry on his job as a



shipping clerk because of inability to concentrate on his work. Significant findings on complete examination were as follows: Blood pressure 170 mm. Hg, systolic and 110, diastolic; peripheral, aortic, and retinal arteriosclerosis, grade II. Renal function was normal. Blood Wassermann and spinal fluid Wassermann reactions were negative. Testosterone propionate was administered by intramuscular injection for 8 weeks. At the end of this time he could think clearly and carry on his work with efficiency; headaches still occurred but were much less severe; the blood pressure was 150 mm. Hg systolic and 90, diastolic. Male hormone therapy was discontinued and he was advised to take, regularly, potassium iodide, aminophyllin, and small doses of phenobarbital. Four months later he began to experience severe headaches again, became extremely nervous and could not concentrate on his work long enough to add up a small column of figures. Two days later he had a cerebral-vascular accident result in paralysis of the right arm and leg. In the course of 3 months recovery from this incident seemed fairly complete although he still complained of headaches, nervousness and difficulty in mental concentration. Male hormone therapy was begun again and two months later the patient felt much improved, being able to do his work satisfactorily. The blood pressure was 155 mm. Hg systolic and 88, diastolic.

#### *Effects on Coronary Circulation*

Twelve patients exhibited characteristic angina pectoris. Of 3 women in this group, 2 were improved on sex hormone therapy, while one individual continued to have frequent attacks of chest pain. Shortly after cessation of treatment this patient died from a coronary thrombosis. Among 9 male patients 7 were definitely improved by testosterone propionate therapy, while 2 individuals were not benefited. One of these who did not improve had a myocardial infarction during treatment with the sex hormones. Improvement, when it occurred, was manifested by an increase in tolerance to all precipitating factors, an increase in strength, and in some cases considerable decrease in the severity of pain when attacks occurred. The response to sex hormone therapy among patients with angina pectoris in this series was not so uniformly favorable as Lesser (4), Bonnell et al. (3), and Hamm (5) obtained.

Five male patients exhibiting attacks of paroxysmal nocturnal dyspnea have been treated with testosterone propionate. One of these individuals had a relatively low blood pressure (100/70). During sex hormone therapy he obtained complete relief from the attacks of cardiac asthma, along with a moderate elevation of the blood pressure (160/90). Of 4 hypertensive individuals 2 obtained definite improvement while 2 were not benefited.

Fifteen patients complained of loss of strength, undue fatigue, and shortness of breath on unusual exertion. A general increase in strength and a specific increase in exercise tolerance occurred in 11 of

these individuals following sex hormone therapy. While dyspnea on unusual exertion is a cardinal feature of early heart failure, actual proof that relief of this symptoms was related to improved myocardial function is obviously lacking. Improved myocardial nutrition incident to an augmentation of coronary flow, however, may have been the effective mechanism.

#### CASE REPORTS

*O. E. F.*, age, 52, a white male exhibited a typical clinical picture of angina pectoris, chest pain being routinely precipitated upon walking 3 blocks. He also complained of recent loss of strength, undue fatigue and insomnia. The blood pressure was 170 mm. Hg systolic and 110, diastolic; the peripheral arteries showed slight thickening; tonsils were enlarged and chronically infected. Electrocardiogram, teleoroentgenogram and other essential laboratory studies yielded normal findings. This man was studied for 18 months in the clinic during which time the tonsils were removed and he received, continuously, potassium iodide, theobromine, and phenobarbital. At the end of this period he complained that attacks of angina were more severe and more frequent. The blood pressure was 165 mm. Hg systolic and 100, diastolic. Potassium iodide and theobromine were discontinued. In the following 3 months he regularly received injections of testosterone propionate. The resulting subjective improvement was marked. He obtained sufficient relief from the attacks of pain to accept a job at light labor and was able to carry on this work without discomfort. At the end of the period of treatment with the androgenic substance, the blood pressure was 125 mm. Hg systolic, and 85, diastolic. He continued to work and 5 months later reported rare attacks of chest pain which he thought could be precipitated by walking a distance of 8 blocks. The blood pressure was 130 mm. Hg systolic and 90, diastolic.

*L. L. K.*, age 58, male white whose complaint was deep aching chest pain radiating to left shoulder; this discomfort was always precipitated by unusual exertion; it was frequently induced by emotional upset, and rarely came on while at rest. He further complained of intermittent claudication in the calf and thigh muscles of both legs precipitated by walking one-half block. The past medical history revealed that 5 years before he had suffered a severe attack of chest pain followed by faintness, cyanosis and marked sweating. This attack was diagnosed as myocardial infarction; he gradually improved and felt normal again 6 months later.

Essential findings on physical and laboratory survey were generalized arteriosclerosis, marked impairment of the circulation of both lower extremities, with cyanotic, cold feet. The posterior tibial pulsation could not be elicited in either foot, while the dorsalis pedis pulsations were barely perceptible. The blood pressure was 120 mm. Hg systolic and 80, diastolic. The electrocardiographic curves were normal. Testosterone propionate therapy was instituted along with mild sedation. After one month of treatment the patient complained that attacks of chest pain were more severe and more frequent. Treatment was continued and 2 weeks later he was seized with a brief,

severe, headache and dizziness followed shortly afterward by paralysis of the left arm. He was hospitalized and treatment with male hormone continued. Three weeks later he had regained the use of the left arm but complained of substernal pain on the slightest exertion. A few days later he was seized with a severe chest pain which lasted 18 hours, a subsequent electrocardiographic tracing clearly indicated a recent infarction of the anterior heart wall.

Mrs. P. E. L., age 63, a white female, complained of a crushing, substernal pain radiating to the base of the neck and down the left arm. This discomfort was always precipitated by walking up one flight of stairs, by anger or excitement, and frequently occurred after a heavy meal. Physical examination and the laboratory survey substantiated the diagnoses of hypertensive and atherosclerotic cardiovascular disease with angina pectoris. The blood pressure was 170 mm Hg systolic and 100, diastolic. During the next 3 months the patient followed a medical program including a), partial bed rest, b), maintenance diet, low in cholesterol and fat, c), aminophyllin 3 grains, 3 times a day, or 5 grains of phenobarbital 3 times a day, and d), nitroglycerin for relief of attacks. At the end of this time she felt somewhat improved, anginal attacks occurring only when she walked 4 blocks or climbed 2 flights of stairs. The blood pressure was 160 mm Hg systolic and 95, diastolic. In the following 3 months the only medication the patient received was estrogenic substance, placebos being substituted for the aminophyllin and phenobarbital. During and at the end of this program of treatment she obtained complete relief from the anginal attacks and was able to walk two miles without untoward effect. The blood pressure at the last visit was 140 mm Hg systolic and 90, diastolic.

#### Effect of Peripheral Circulation

Fourteen patients with organic peripheral vascular disease were treated with androgenic and estrogenic substances. In this group 8 individuals showed marked improvement, 2 responded fairly well, and 4 were not benefited. In 2 patients, with characteristic thromboangiitis obliterans, the results were unusually good. In the atherosclerotic group, 2 female and 4 male patients showed definite improvement, while 2 men were relieved of pain but still presented objective evidence of impaired circulation. Three men and one woman in the atherosclerotic group were not obviously helped by the treatment with androgenic or estrogenic substance. In all 4 of these who showed no improvement vascular involvement was extensive.

#### CASE REPORTS

J. N. L., age 40, white male. This patient complained of severe claudication in the left calf after walking 4 blocks, and painful ulcers on the left great and fourth toes. Claudication had begun 3 years before and the ulceration was of 2 months' duration. Both feet and lower legs were cold and cyanotic. Cyanotic rubor appeared on dependency and unusual blanching on elevation. Gangrenous ulceration involved the tip of the great toe and

the distal one half of the fourth toe. No pulsations were demonstrable in the pedal arteries of the left foot, the left popliteal, and the right posterior tibial. Ossilometric indices were: Left ankle,  $\frac{1}{2}$ , just below left knee, 2, left mid thigh, 3, right ankle, 1, just below right knee, 3, right mid thigh, 5. Active phlebitis was present in the right leg. Treatment consisted of male hormone only. At the end of 4 months the ulcer on the great toe had healed, the fourth toe had sloughed off and the stump had healed. The patient could walk 5 miles without pain. The color and apparent temperature (by palpation) of the feet and legs was much improved, although moderate cyanosis was still demonstrable on dependency, and unusual blanching on elevation. The ossilometric indices were: Ankle,  $2\frac{1}{2}$ , just below left knee, 4, left mid thigh, 4; right ankle, 3, just below right knee, 4, right mid-thigh, 5.

L. T., age 73, a white male, complained of continuous excruciating pain and ulceration of the right foot. He had experienced pain in the calf of the leg on walking for the previous 2 years, and had been unable to keep his feet warm in cold weather for the past 5 years. The entire right leg was cold and slightly cyanotic. There was an area of deep ulceration involving the plantar and lateral aspects of the right foot at the base of the small toe. Pulsations were not palpable in the pedal, popliteal, or femoral arteries of the right lower extremity. Ossilometric indices were: right ankle, 0, just below right knee, 0, mid thigh  $\frac{1}{2}$ . Male hormone was administered by intramuscular injection. This therapy was continued for 2 months without any evidence of improvement. There was no relief from the pain and the gangrenous ulcer was larger at the end of treatment than it had been in the beginning.

#### DISCUSSION

In an attempt to evaluate a given chemotherapeutic substance in the treatment of primary hypertension one is faced with the difficult task of distinguishing between the psychotherapeutic and the pharmacodynamic properties of the remedy in question. The physiological background for so called essential hypertension probably is an inherent neurogenic defect which, prior to the establishment of irreversible vascular changes, is manifested by unusual vasomotor irritability (9, 10). While it is well known that these individuals exhibit an exaggerated vasoconstrictor response to disagreeable psychic stimuli, it is often overlooked that agreeable psychic stimulation can provoke the opposite vasomotor reaction with a consequent fall in blood pressure. This highly susceptible neurovascular mechanism accounts for the fact that some lowering of the blood pressure along with subjective improvement can be effected in patients with essential hypertension by almost any therapeutic procedure which includes, among its more pertinent features, a liberal measure of reassurance.

While psychotherapy unquestionably has played an important rôle in this study, certain findings indicate that the sex hormones exert a definite and a sustained vasodilating action. The majority of the

patients in this investigation were being treated by other methods when sex hormone therapy was initiated, and in many of these a further lowering of the blood pressure occurred. In the entire group of hypertensive individuals, sex hormone therapy has resulted in a more pronounced and more prolonged lowering of the blood pressure than I have usually obtained by other medical methods. Moreover, the effect of these substances in occlusive peripheral vascular disease and angina pectoris is further indicative of a pronounced vasodilating action.

Subjective improvement among these patients has been more evident than is usually observed as a result of other therapeutic methods. Such phenomena are difficult to evaluate since they are not amenable to any known accurate method of study. Nevertheless, relief of distressing symptoms is a highly desirable result and, alone, may be conducive to further vascular relaxation. Hamm has discussed this point briefly and excellently (5).

The data presented in this study favor the concept of a direct vasodilating action of the sex hormones. This is a reasonable explanation of the relief of vasospastic cerebral phenomena, improvement in the anginal syndrome, the favorable effect on the peripheral vascular system, and the fall in blood pressure in some hypertensive patients. A direct vasodilating action is not, however, in keeping with the fact that the blood pressure is occasionally elevated in hypertensive individuals as a result of sex hormone therapy; nor will it explain the usual failure of these substances to affect the normal blood pressure (2, 11, 12). In a consideration of the menopausal syndrome it is difficult to explain the variety of vascular disturbances which occur in this manifestly hypogonadal state entirely on the basis of deficiency of a hormone whose essential vascular action is vasodilation (13-16). It is consistent with the known facts concerning vasomotor instability in the climacteric to reason that gonadal dysfunction may produce an endocrine imbalance which, shifted in one direction provokes vasoconstriction and, shifted in another, causes vasodilation. While the gross mechanism by which the sex hormones favorably influence vasospastic phenomena is obviously vasodilation, the finer mechanism may be the establishment of an endocrine balance.

The findings in this survey strongly suggest that the sex hormones are useful chemotherapeutic remedies for the management of patients with essential hypertension, angina pectoris, and peripheral vascular disease. The utility of the androgenic and estrogenic substances in cardiovascular disease appears to be directly related to the property of these substances for effecting vasodilation.

## SUMMARY

1. The pertinent literature on the use of the sex hormones in cardiovascular disease is briefly reviewed.

2. Results in the treatment of 82 individuals with androgenic and estrogenic substances are reported; these patients exhibited the following clinical syndromes: 56 patients had essential hypertension; 12 had angina pectoris; and 14 had organic peripheral vascular disease.

3. The results are briefly discussed, attention being directed to the probable psychotherapeutic as well as pharmacodynamic properties of the sex hormones.

4. The sex hormones appear to be valuable chemotherapeutic substances in essential hypertension, angina pectoris, and organic peripheral vascular disease.

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# Sublingual Administration of Diethylstilbestrol; Comparison of Routes in Therapy

## [[Estrogens and Menopause]]

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DESPITE THE FACT that diethylstilbestrol is highly effective as an estrogen when taken orally, in certain instances other routes of administration may be preferable. Intramuscular injection may be the treatment of choice in some cases when termination of lactation is desired, when large doses must be given and the duration of treatment is short. Injection will seldom be the method of choice for maintenance therapy because of the inconvenience, pain and greater expense as compared to the oral route. Subcutaneous implantation of pellets is practical and effective, as we have previously reported (1), but is preferred by only a small percentage of patients. It is desirable also to be able to interrupt estrogen therapy easily and at will. There is much evidence to suggest that regularly interrupted or cyclic administration of estrogen may prove to be the most logical mode of therapy, and to give the best clinical results (2).

Certain hormones are absorbed quickly into the sublingual venous plexuses. In the instances of desoxycorticosterone (3) and estradiol (4, 5) the demonstration that the sublingual route is effective is of considerable importance, because of the very poor absorption of these substances from the gastrointestinal tract and their consequent oral inefficacy. Although this indication for trying sublingual therapy with diethylstilbestrol does not exist, we decided to study the response of patients to treatment by this route, a), to determine the relative effectiveness of the sublingual as compared with the oral and intramuscular routes, b), to provide an alternative method for patients who dislike swallowing tablets, c), to determine whether the incidence of nausea as compared with that following oral therapy might be diminished.

### METHODS

Seventeen women suffering from typical symptoms of estrogen deficiency were chosen for this study. The chief complaints were similar in all of these cases and were chiefly hot flushes, headaches, nervousness, fatigue, insomnia and emotional instability. The cause of the hypoestrinism was spontaneous menopause in 12 of the 17, removal of the ovaries in 4, and radium therapy to the pelvic organs in 1. Two of the patients were over 50 years of age, 8 were between 40 and 50, 6 between 35 and 40, and 1 under 35.

Diethylstilbestrol in propylene glycol (20 mg to the cc) was administered by dropping the solution under the tongue with a medicine dropper. The droppers used delivered 40 drops to the cc, so that 1 drop twice daily, for example, gave a daily dose of 10 mg. Patients were cautioned not to swallow the material, being instructed to spit out any excess fluid present in the mouth after allowing 4 minutes for absorption. The dose used in most cases was 2 drops daily for 2 weeks, followed by a 2 week interval without medication, with regular repetition of the cycle. In a few patients 4 drops (20 mg) daily were given for the 2 week period. A few patients required longer periods of treatment, and shorter intervals without medication to insure good relief of symptoms. Results were judged by a), the relief of symptoms, and b), the changes in the vaginal smears. No patient is included in this analysis who was not treated with the drops for at least 1 month. Five were treated for 3 months, 4 for 6 months, 1 for 9 months, 1 for 14 months.

### RESULTS

Good relief of symptoms was obtained in 11 of the 17 cases. In judging the degree of relief, comparison

<sup>1</sup> Diethylstilbestrol in propylene glycol was supplied by the Department of Medical Research of the Winthrop Chemical Co., 170 Varick St., New York City.

was made with the improvement following oral diethylstilbestrol therapy or parenteral administration of the natural estrogens to the patient during other periods of study. The degree of symptomatic relief was poor in 6 cases. In 4 of these 6 cases nausea was so troublesome that treatment was discontinued. Eight of the 17 patients experienced nausea at some time during the course of sublingual therapy. In 3 instances this was temporary and good results without nausea were obtained with continued treatment. We have never encountered such a high incidence of nausea with orally administered diethylstilbestrol, our figures being 20 per cent for continuous medication, but only 8.6 per cent with the interrupted method (2). Nausea was sufficient to make sublingual therapy impractical in 5 of the 17 cases, or 30 per cent, even when the mode of interrupted treatment was used. It seems likely that the unpleasant taste of the material may have increased the frequency of this symptom.

Vaginal smear response was definite in all cases, the estrogenic effects of the material administered sublingually differing little from that obtained by the same doses given orally. Sublingual therapy proved to be no more effective per milligram administered than when given by the oral route, as judged by the effects on the vaginal smears. One mg. per day by mouth is approximately equivalent to 1.0 mg. per day when given sublingually or 0.5 mg. intramuscularly, as judged by 'human assay' as performed on this and previous groups of our patients.

Of the 11 patients obtaining good results, 1 required continuous therapy with 1.0 mg. sublingually. She has taken this steadily for over 14 months. This patient had had an artificial menopause produced by radium 3 years before onset of treatment. Her menopausal symptoms had been so severe that she was unable to obtain and hold a job even though it was economically necessary for her to do this. Hot flashes would occur 3 to 4 times nightly, and would be strong enough to waken the patient and disrupt sleep. Nervousness was acute; she was unable to talk without a quaver in her voice, was unable to mix and talk with people without crying. Partial relief had been obtained with the use of diethylstilbestrol in tablets,

but the severe nausea encountered made it necessary for the patient to interrupt treatment so often that the vaginal smear rarely changed to more than 1+. However, she was able to take the drops continuously without nausea. The vaginal smear changed from 0 to 4+ and has remained so until the present time. She has now secured and holds a fairly good position and has become socially adjusted again.

Two patients required 4 drops (2.0 mg.) daily for 2 weeks, when alternated with a 2-week period without treatment, while 6 patients did well with 2 drops (1.0 mg.) on this schedule. Two patients did best when the drops were given for 3 weeks, and omitted for only 1 week. No other untoward symptom and no evidence of toxicity except nausea was observed in any of the 17 patients.

#### SUMMARY

1. Diethylstilbestrol in propylene glycol administered sublingually gave a positive vaginal smear response in all of 17 cases of hypo-estrinism.
2. Relief of symptoms was good in 11 cases; poor in 6.
3. The chief cause of failure of symptomatic improvement was nausea. Nausea occurred much more frequently with sublingual than with oral therapy.
4. Per milligram of the diethylstilbestrol administered, sublingual therapy is approximately equivalent to oral therapy while intramuscular injection is approximately twice as effective.
5. In a small percentage of patients sublingual diethylstilbestrol therapy may prove preferable to the oral or intramuscular routes, or to pellet implantation. Oral administration remains the treatment of choice in the great majority of patients.

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# A Spermatozoal Stain for Clinical Studies<sup>1</sup>

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NUMEROUS methods have been described for staining human spermatozoa. Some of these produce excellent results. As a rule, however, the methods which give the best results require several hours or days for completion. This fact makes them more suited to research problems than to clinical studies.

Technicians not uncommonly experience difficulty in reproducing results when employing the staining methods of other workers. In our laboratory we have not been able to produce satisfactory stains with any one of several generally accepted clinical methods for staining smears of human seminal fluid. We have developed, therefore, a method for clinical use which has proved satisfactory in our hands. This report presents the details of this method.

## METHOD

Smears of the seminal fluid are made, as soon as the specimen has liquefied, by drawing a drop of seminal fluid over a glass slide with the end of another slide. The smears are fixed by passing the slides several times through a flame. Staining may be done at this point, or the smears may be stored for future study.

Three stains are utilized,<sup>2</sup> two of which are to be found commonly in the clinical laboratory. These two are hematoxylin and eosin. The third stain, fast green, is readily available although it is not in general use.

## PROCEDURE

After the smear is fixed with heat, the staining technique proceeds throughout in Coplin jars as follows:

- 1) Let stand in 95% alcohol<sup>3</sup> 5 to 10 minutes
- 2) Wash out excess alcohol in tap water
- 3) Stain for 1 minute in Harris' hematoxylin (Harris' hematoxylin, 1 part, 8% alcohol, 3 parts). In making up the original stock solution of Harris' hematoxylin, 4 cc. of glacial acetic acid are added to 100 cc. of stain.

- 4) Rinse out excess hematoxylin in distilled water
- 5) Destain 5 to 7 seconds in acid alcohol (concentrated hydrochloric acid, 1 cc., 95 cc. of 70% alcohol)
- 6) Rinse thoroughly in distilled water
- 7) Transfer to weak alkaline water (ammonium hydroxide, specific gravity 0.90, 2 drops, tap water, 60 cc.) for 5 to 10 seconds
- 8) Rinse in distilled water
- 9) Counter-stain in eosin (eosin 'Y,' 1 gm., 25% alcohol, 95 cc.) for 3 minutes
- 10) Rinse quickly in distilled water
- 11) Counter stain in a 1% aqueous solution of fast green for 15 to 20 seconds
- 12) Rinse in 95% alcohol, leave stain streaking on slide
- 13) Rinse in absolute alcohol until, upon gross inspection, the green dye has been washed out. This is a matter of a few seconds
- 14) Clear for 3 minutes in xylol
- 15) Mount in balsam

The spermatozoa are differentiated by this stain as follows: acrosome, lavender; nucleus, pink; body and tail, green. The technique requires less than 25 minutes to execute.

## DISCUSSION

There are but few critical steps in this staining procedure. The fast green has a tendency to wash out the eosin. It is advisable, therefore, not to rinse the smear too thoroughly between the eosin and the green dye, nor to leave the smear longer than the stipulated time in the solution of fast green. Occasionally, smears made of seminal specimens which are particularly mucoid are difficult to stain satisfactorily. Such a smear can be stained with some success if first Williams' (1) method of mucus liquefaction is applied.

A high percentage of seminal fluids contain spermatozoa which are morphologically normal in appearance, but which are not stained by this method. Multiple smears made from the same seminal specimen show approximately the same percentage of these spermatozoa. The percentage varies greatly between seminal specimens. The significance of this finding is being studied.

We have found that smears which have been stored for several weeks stain as well as freshly made ones,

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<sup>1</sup> Part of the expenses of this study was defrayed by a grant to one of us (M. B.) from the Research Council of Duke University.

<sup>2</sup> The hematoxylin-eosin Y and fast green (certified) were obtained from the National Aniline and Chemical Co., Inc., New York City.

<sup>3</sup> No methanol is used in this method.

and that smears made from seminal fluid which has been refrigerated several days also stain well.

This method of staining smears of seminal fluid has several features which are of some importance to the clinician. *a*). The procedure may be completed in 25 minutes or less. *b*). Results can be duplicated by technicians unfamiliar with the procedure. *c*). Spermatozoa are stained differentially with regard to their morphologic characteristics. *d*). Freshly prepared smears or old ones stain equally well. *e*). Readily obtainable stains are employed.

#### SUMMARY

A staining method is described for use in clinical studies of human seminal fluid. Harris' hematoxylin and the counterstains, eosin-Y and fast green are employed. The spermatozoa are differentiated morphologically. The technic requires less than 25 minutes to complete.

#### REFERENCES

1. WILLIAMS, W. W.: *New England J. Med.* 217: 946. 1937.



## COMMUNICATIONS TO THE EDITORS

### Treatment of Amenorrhea with Diethylstilbestrol and Chorionic Gonadotropin\*

AMENORRHEA, whether primary or secondary, is still a major therapeutic problem. With rare exceptions organotherapy has failed to elicit permanently good results. At best, bleeding is induced upon withdrawal of the experimentally administered hormone without, however, sustained cyclic menstruation thereafter. The ideal treatment has not been attained, because the etiology of amenorrhea remains unknown.

Recently Pencharz<sup>1</sup> reported maximum stimulation of the immature rat ovary with chorionic gonadotropin combined with diethylstilbestrol. The stimulation exceeded that of any other experimental hormonal stimulus. This combination of hormones was, therefore, given to 12 amenorrheic women in the hope that such therapy might effect more permanent results than were attained with cyclically administered sterols or with equine gonadotropins. The latter hormones had previously yielded very indifferent results in this clinic.

Of the 12 patients, 4 complained of primary and 8 of secondary amenorrhea; only 8 were treated and observed long enough to warrant reporting. All of these patients were sterile.

**Method.** In addition to the usual routine clinical data, urinary bioassays for gonadotropins (FSH) and estrogens, as well as endometrial biopsies were made before and 2 weeks after therapy was completed. These hormones were determined on 7 to 10 pooled specimens of 12-hour night urines. The estrogens were estimated by modifications of existing methods of assay on spayed adult rats. The gonadotropin was determined by the Zondek alcohol-precipitation method, using immature mice. Vaginal canalization, Graafian follicle stimulation, and vaginal cornification was taken as a positive response. Some pregnandiol determinations were made according to the method of Venning and Browne.

The B.M.R. of all of the 12 patients was below normal, varying from  $-15$  to  $-38$ . Accordingly, thyroid extract was prescribed in doses of  $\frac{1}{2}$  to 2 grains daily with weekly intermittence each month to avoid cumulative effects.

Oral diethylstilbestrol was given, usually for 2 weeks in each month in 1 to 2 mg daily doses, the lesser dosage being reserved for those who complained of nausea or other side reactions.

Chorionic gonadotropin (APL) was injected twice or thrice weekly in doses varying from 500 to 1000 i.u. for

2 months, after which injections were stopped for one month to lessen the possibility of anti-hormone effects.

A treatment schedule of 6 to 12 months in the above fashion was deemed an adequate trial.

**Results.** No severe side reactions were noted in any patient. Occasional headaches were induced and it was not clear which of the two hormones was responsible.

The essential diagnostic and therapeutic data are depicted in the accompanying table.

No striking advantages can be claimed for this trial therapy as compared with cyclically administered sterols or other gonadotropic treatment. One patient with primary, and 2 patients with secondary amenorrhea, have continued to menstruate from poorly developed endometria at long and irregular intervals, but not without occasional supplemental therapy with oral estrogens, such as diethylstilbestrol or the naturally conjugated estrogens†. The other patients were wholly refractory to treatment. Infertility was not influenced. Bioassay yielded no data of striking diagnostic or therapeutic significance.

Most of the values before and after the experimental treatment fall within normal limits. It is apparent, however, that the increased estrogenic titers following therapy were not of the same high level as seen at the mid or premenstrual phases of the normal cycle. In one case treatment seems to have actually depressed the values for estrogens. The values for the pituitary gonadotropic factor were not significant. They did not attain castrate nor menopausal levels. The experimental therapy did suppress FSH excretion in 3 cases.

The endometrium showed increased proliferation in all cases but never progesterational reaction.

**Comment.** Most of the evidence here and elsewhere points to ovarian and endometrial refractivity to hormonal stimulation and until this refractory state is better understood, the problem of amenorrhea remains unsolved. It is apparent that fair amounts of circulating hormones may activate an atrophic endometrium, but this does not stimulate a true menstruation. It is possible that more concentrated dosage would have elicited better responses. But here again the intangible factors of variability of organ or species response to hormonal stimulation complicate the question of adequate dosage. This clinical experiment again emphasizes the fact that laboratory observations are not necessarily applicable to the human subject.

† The natural estrogen (Premarin) was supplied by Ayerst, McKenna and Harrison, Rouses Point, N.Y.

Histological preparation and interpretation of the endometrial biopsies by Dr. J. Tragerman is gratefully acknowledged.

\* This study was supported by a grant from Ayerst, McKenna and Harrison, Ltd.

<sup>1</sup> Pencharz R. I. *Science* 91: 554, 1940.



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# Androgen Therapy in Women

## TO THE EDITOR

FADS AND FASHIONS always have characterized the practice of medicine, indeed, even diseases are not free from these vagaries, as our old Professor of Medicine observed in a paper on 'Fashions in Typhoid Fever,' but unfortunately clinical endocrinology in recent years has had more than a healthy share of these. The past 12 years have seen extravagant therapeutic excursions involving the use of chorionic gonadotropin, equine gonadotropin and now the currently popular ones, androgens and diethylstilbestrol.

The organotherapeutist of several decades past did little harm and dubious good with his glandular potions regardless of his ardent empiricism or the woeful paucity of his pretherapeutic diagnostic endeavors. Now, however, there is not the same immunity for the careless or unscientific therapeutic enthusiast. Many of the currently available endocrine preparations are powerful pharmacodynamic principles, which, depending upon the skill of the clinician, may be implements for the repair of damaged glandular systems or may act as tools for wrecking completely the physiologic economy of patients.

The recent widespread employment of androgens in the treatment of many of the functional aberrations and organic diseases of women's gynecic system has gone too long un denounced as a deplorable example of highly dangerous empiricism. When carefully controlled scientific studies of the pharmacologic effects of androgens upon women were being reported by competent workers, there was the obvious justification that here was a new scientific gimmick which was yielding stimulating experimental data. At the present time, however, with pharmaceutical concerns widely advertising androgens for use in gynecic disorders in this and other journals, conscientious and scientific clinicians cannot continue to dismiss placidly this victimization of women as being the result of natural 'growing pains' of a new science.

Despite the fact that, as yet, careful clinical studies have failed to identify a single syndrome in women due to a hypo-androgenic state, and regardless of the fact that no generally acceptable proof has been advanced as to the physiologic rôle of androgens in gynecic endocrinology, androgenic therapy continues to be a common practice. Why is this, we ask. Is it because clinicians find themselves unable to resist the commercial solicitations of pharmaceutical chemists who, having male hormones to sell, but embarrassed by such a limited field in andrologic practice, insist that these be used in gynecology?

Androgens have come to be used inseparably with estrogens under diverse circumstances, including prolonged and excessive uterine bleeding, menopausal symptomatology, undesired lactation, menstrual migraine, dysmenorrhea, cyclomastopathy, et cetera. Equally as good, and often better, symptomatic responses have been obtained in these conditions from the use of estrogens. The rationale of risking grave virilization sequelae from unnecessary androgenic therapy is incomprehensible.

Androgenic therapy is admitted by its proponents to produce for the most part 'ovarian negating' responses

the therapeutic implication that these conditions are hypovarian ones? Most conservative gynecologists realize the need for adequate implements capable of stimulating hypofunctioning ovaries, upon the existence of which so many gynecologic aberrations are predicated. Wherein does there exist the need for the further depressing of these hypofunctioning ovaries?

Aggravation of ovarian failure, while a cogent contra-indication to the use of androgens in most gynecologic states, is not the gravest of these contra-indications. The most serious complication of androgenic therapy in the female is the cosmetic and contra-sexual mutilation which it may produce. Any clinician practicing endocrine gynecology sees far more hirsute women than he can depilate, in fact, far more than he can conscientiously offer any therapeutic hopes. Why should this number be increased willfully by unnecessary therapy?

It may be argued that these virilization phenomena, if they do appear during androgenic therapy, will disappear upon its discontinuation. Some of these may disappear; others are irreversible. The excessive hair may fall slowly following cessation of therapy, all may not disappear. The laryngeal changes, responsible for the throaty, husky voice, do not leave the individual.

Some workers have justified the production of these distressing pseudohermaphroditical signs upon the basis of the therapeutic results obtained, i.e., relief from endometriosis, and shrinkage of fibromyomatous tumors. Admitting the fact that some gynecologists are possessed of a *future operantius*, and that under these circumstances, conservative endocrine therapy has been a boon to many women, surgery for endometriosis and for fibromyomata seems far more conservative than contra-sexual hormonal mutilation of the woman.

This writer has seen a number of pathetic examples of unjustified androgenic therapy. The most pathetic and flagrant of these cases was the following:

The patient, a 25 1/2-year-old girl, was seen by a neurologist because of progressive muscular weakness of 2 1/2 years' duration. His diagnosis was that of progressive muscular dystrophy of the Landouzy-Dejerine type. The patient was referred by him to the writer because of a strange history of androgenic therapy having been employed previously and because of the obvious contra-sexual effects of this. The endocrine record was as follows:

The patient's adolescence had been normal. Menarche had occurred at 11 years of age. Sexual maturation had been normal. Menses had continued regularly and without abnormal symptomatology until one year previously when the patient consulted a physician who is said to have started her on androgenic therapy. She is said to have received 25 mg. of testosterone propionate intramuscularly every 3 to 4 days for 10 months. One severe menstrual period occurred following the cessation of therapy. No further menses occurred. The patient's voice became so husky she could hardly talk. There was noticeable enlargement of the breasts. There was some increase in body hair and facial hair became worse.

A wise family physician stopped the androgenic therapy before the patient was seen by the writer. Six months after treatment was discontinued, the patient's hair had returned to normal, the voice was normal, the breasts had returned to normal, and the facial hair had disappeared. The patient was then treated with estrogens, and the hirsutism, slight hypothyroidism, and the enlargement of the breasts were relieved.

The only apparent foundation which the patient's physician had for initiating androgenic therapy of this little girl, who was obviously normal from a gynecologic and endocrine point of view, must have been that he had been told that androgens, among their various other pharmacologic properties, possessed the ability to stimulate the volume of skeletal muscles. It goes without saying that the androgenic therapy given this patient had no effect on her Landouzy-Dejerine paralysis.

From these considerations it seems obvious that any

androgenic therapy of woman, regardless of what its presumed foundations may be, should be considered contraindicated and that, when this therapeutic approach be embarked upon, the patient is exposed needlessly to possible pharmacologic mayhem.

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# The Journal of CLINICAL ENDOCRINOLOGY

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## Clinical Reviews in Andrologic Endocrinology:

### [[Testicular Dysfunction]]

#### I. Physiology, Functional Pathology and Diagnosis

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THERAPY of deficient testicular function is indicated chiefly for two reasons, a), the rational treatment of various hypogonadal states in which alterations of body habitus assume clinical importance, and b), the correction of seminal inadequacy which impairs fertility. The internist, urologist and endocrinologist usually originate and supervise the therapeutic approach to the former group, the gynecologist, as a part of the gynecologic and andrologic investigation of barren couples, usually initiates investigation of the fertility of husbands.

Professional contact is established when the wife of one of these couples seeks the gynecologist's advice as to why she has not become pregnant. Since, as a rule, the husband has not considered the likelihood of his sexual function being at fault, the responsibility of orienting him as to the necessity for, and the scope of his examination usually falls upon the gynecologist. Frequently, the seminal studies must be made by the gynecologist or his trained assistants rather than relying upon the urologist for these data, this fact often closely associates the gynecologist with the results of any therapeutic en-

deavors which may be necessary in the husband's case. His counsel is sought by the husband and by the wife as to the prognosis, when all of the diagnostic data have been collected. Good sound clinical judgment of the gynecologist may prevent unwarranted therapeutic exploitation of husbands by overly endocrine-conscious consultants.

In the fertility group, symptoms and signs commonly ascribed to hypogonadism are often lacking, although it is to be recalled that seminal inadequacy, either relative or absolute, is manifested in both groups of patients. For orientation, therefore, review of seminal and endocrine physiology of the testes, endocrine pathology and the diagnosis of gonadal levels of function is pertinent.

#### ENDOCRINE PHYSIOLOGY

The physiologic rôle of the testes is a two fold one, a), to produce an abundance of healthy spermatozoa for the fertilization of ova, and b), to supply a hormone, testosterone, capable of producing growth, differentiation and functional adequacy of normal adult sexual apparatus.

Spermatozoa develop from the spermatogonia of the seminiferous tubules. Testosterone is thought to be

secreted by the Leydig cells in the interstices of the testis. Both the seminal epithelium and the interstitial elements, i.e., the exocrine and the endocrine functions, are dependent for normal activity upon the gonadotropic influences of the anterior lobe of the pituitary. It has been assumed generally that the gonadotropic complex which is responsible for luteinizing phenomena in the female is concerned with tropic influences upon the interstitial elements of the testis while that complex which governs follicle maturation in the female produces stimulation of the germinal epithelium of the male.

These gonadal-pituitary interrelationships have been established from experimental data secured by studies upon laboratory animals. Some generalizations from these data are: a), Removal of the pituitary produces testicular atrophy which involves both interstitial and germinal elements. b), Castration results in hyperactivity of gonadotropic function of the pituitary, associated in some species with characteristic cytologic alterations of the gland. c), Implants of pituitary glands or injections of active gonadotropic extracts repair post-hypophysectomy damage, if this has not proceeded too far or existed too long. d), Implants of testis or injections of active androgenic extracts (or crystalline testosterone or its esters) restore normal pituitary function after gonadectomy.

Van Dyke (1), however, has summarized data which conflict with the generally accepted concept of biphasic specificity of the pituitary gonadotropic complexes. a), Either factor of the gonadotropic complex will support spermatogenesis in mature hypophysectomized male rats but the luteinizing fraction is necessary for maintenance of the interstitial cells. b), In the same test animal, spermatogenesis can be maintained if androgens are given promptly after hypophysectomy. c), The pituitary of the intact male rat apparently secretes only the follicle-stimulating fractions, although small amounts of the luteinizing fraction have been encountered after implantation of pituitary tissue in this animal.

Increases in the gonadotropic activity of the pituitary produce increased testicular activity which results in the outpouring of additional testosterone, the effect of which is to depress pituitary function. On this basis the existence of another hormone, thought to be produced by the germinal epithelium and to be concerned with the regulation of the tropic effects of the pituitary upon this epithelium, has been suggested by some investigators. Despite some supportive evidence from clinical and laboratory data factual proof that the testis secretes a second hormone has not been advanced.

Clinical observations support these concepts of gonadal-pituitary interrelationships. Gonadal failure,

both exocrine and endocrine, is common in pituitary disease, i.e., adiposogenitalism, pituitary dwarfism, pituitary cachexia and basophilism. The grades of hypogonadism which are associated with various alterations in pituitary function have not been defined as clearly as desirable, in regard to either germinal or endocrine levels of function. The clinical findings in severe grades of pituitary failure, however, are striking and unequivocal.

Thyroid-gonadal interrelations have been delineated even less clearly. The good therapeutic results which follow the 'empiric' use of thyroid substance in patients of both sexes with lowered fertility support the belief that close integration of the functions of the thyroid and gonads exist. On the contrary, hypometabolism may exist in individuals of either sex with little demonstrable evidence of endocrine or germinal impairment (2).

Experimental data from laboratory animals indicate that, as a rule, disturbances in thyroid function impair spermatogenesis. Some animals, as Moore (3) has observed, appear to be singularly independent of the thyroid in this regard, i.e., the frog tadpole (Allen, 1918, quoted by Moore) and the immature rat (Ross, 1936-1938, quoted by Moore). Moore has concluded from a review of the experimental data that no direct relationship has been established between the thyroid and the testis and that good evidence exists that the indirect associations are mediated by way of the alterations in metabolism.

While pertinent interrelationships of the thymus and pineal with testicular function have been suggested, only the pituitary has been proven to have a dominant rôle in the sexual physiology of the male. Normal sexual function requires an adequate level of general health so that diseases or functional alterations in any of the glands, as well as chronic or acute constitutional diseases, inanition, avitaminosis and intoxications induce alterations in testicular function; these, however, are, for the most part, indirect rather than direct influences upon the endocrine system.

#### ENDOCRINE PATHOLOGY

Alterations in testicular function may arise from diverse causes; failure may result from intrinsic inadequacy of the gonads or from damage produced by disease or trauma; it may be secondary to disturbances in other endocrine glands or it may be due to secondary depressing effects of constitutional disease or impairment. These various etiologic factors produce fluctuations in the gonado-pituitary reciprocities, important elements of which are levels of hormonal secretion and receptivity or responsiveness of end organs.

Gonadal failure may be of two types; it may embrace both the endocrine (interstitial) and exocrine

(seminal) functions, or it may be characterized by seminal failure alone. No clear-cut instances of endocrine failure with persistence of normal germinal activity exist. A suggested classification for gonadal failure is the following one.

#### I Androgenic and seminal failure (hypogonadism)

- 1 Intrinsic or primary in gonads
  - a Adolescent hypogonadism due to embryologic faults or disease
  - b Senile hypogonadism
  - c Hypogonadism due to acquired disease (orchitis) or tumors
  - d Surgical or roentgenologic hypogonadism
- 2 Hypogonadism, secondary to other disorders
  - a Due to pituitary disease
  - b Due to diabetes mellitus
  - c Due to adrenal disease
  - d Due to causes primarily extra-endocrine in nature

#### II Seminal failure, without androgenic failure

- 1 Intrinsic in gonads due to failure of descent
- 2 Due to thyroid disease
- 3 Due to adrenal disease
- 4 Extra-endocrine, due to toxins, chemicals, high fever and sexual excess

The various alterations in endocrine levels and in end organ responsiveness which characterize these various types of testicular failure are reviewed briefly.

**Intrinsic hypogonadism.** No significant impairment of pituitary function occurs. Due to the absence of the 'conditioning' action of normal androgenic levels, a compensatory hypergonadotropic state in the pituitary may ensue, designed to overcome the characteristic relative non responsiveness or refractory state of the gonads.

A brief consideration of the basic pathology under these circumstances affords little rationale for gonadotropic therapy. Various grades of hypoplasia or aplasia result from embryologic faults or fetal diseases, such as syphilis. Gonads are rarely absent. Hypoplasia involves both germinal and interstitial elements. Small fibrous nodules in the scrotum may constitute the only vestige of gonads.

It is correct to assume, perhaps, that senescent hypogonadism of the male, as in the female, is due to development of an intrinsic refractivity of the gonads, although, as Engle has observed (4), the degenerative changes in the testes are not as striking as those in the ovaries. The increased excretion of gonadotropins in aging man is not as definite as that in the climacteric woman. Despite thickening of the basement membrane of the seminiferous tubules and of the surrounding tunica propria which is probably the results of altered vascularity, evidences of active spermatogenesis have been observed in the testes of

men in the sixth and seventh decades of life. The integrity of the physiologic functions of the seminiferous tubules is accepted generally as evidence of adequate endocrine function of the gonads. While it has been said that the interstitial function outlasts the seminiferous one, the most striking changes of the sexual apparatus in aging occur in the prostate.

Local diseases of the epididymis or the funicular structures, and certain surgical procedures which interfere with testicular circulation, may result in various degrees of testicular fibrosis and atrophy with consequent functional impairment. Orchitis, complicating many diseases, may be followed by varying aberrations. These alterations which are often focal rather than general and involve both the interstitial and germinal elements, include impairment of vascularity, fibrosis and focal necrosis, and hyalinization of the seminiferous tubules. In advanced grades of testicular atrophy, the seminiferous epithelium may be reduced to a state of rather complete degeneration in which only a few Sertoli cells remain. While various drugs and chemicals exert profound gonadopathic influences, these affect, for the most part, the germinal rather than the interstitial elements and are discussed, accordingly, in the consideration of seminal failure occurring without significant endocrine impairment. The functional break in this group of conditions occurs in the end organ or gonad portion of the pituitary-gonad axis with the result that any alterations which may occur in pituitary levels of function are in the order of increases rather than decreases.

Testicular tumors tend to produce seminal and usually androgenic failure. These tumors include those originating in a), connective tissue, fibromata and myomata, or b), seminiferous epithelium, seminomata, and they have no intrinsic endocrine secretion; those originating from c), misplaced or embryonal sex cells, teratomata, chorion epitheliomata, or from d), interstitial tissue, such as adenomata of undescended or atrophic testes, neoplastic-like hyperplasia, these are associated frequently with alterations in endocrine function, such as an increased secretion of gonadotropins, androgens or estrogens. Despite the increased androgenic secretion of some interstitial cell tumors, which may result in precocious adolescence, damage to the seminiferous elements may occur as the result of depression of pituitary function induced by the high androgenic titers. Chorion epitheliomata, causing at times gynecomastia and lactation, may produce atrophy of the uninvolved testes due to the direct action of the large amounts of estrogenic secretion and to pituitary depression. Unilateral testicular tumors of non endocrine nature may cause little apparent endocrine or seminal impairment, if the uninvolved testis is healthy and capable of compensation.

Similar observations characterize the endocrine and germinal pathology which follows roentgenologic damage to the gonads. The early effects of testicular irradiation are on the spermatogenic cells, involving the least differentiated elements, the spermatogonia, and progressing, when severe damage has been inflicted, to a complete destruction of the germinal epithelium except, perhaps, for a few Sertoli cells. When there has been heavy irradiation, the interstitial elements are destroyed and fibrous atrophy of the testes ensues.

*Hypogonadism, due to pituitary disease.* Clinical syndromes resulting from pituitary disease are characterized generally by hypogonadism. No initial intrinsic aberrations occur in the gonads as regards their responsiveness, although, as Van Dyke (1) has observed, some experimental studies indicate that even a short period of pituitary deficiency may lessen markedly their sensitivity to therapy. Under these circumstances, it would seem likely that promptly initiated and adequately administered gonadotropic therapy might be able to restore normal gonadal function.

Hypogonadism may characterize some syndromes in which hyperactivity of certain functions of the pituitary exist, i.e., acromegaly and gigantism. Several explanations have been suggested for this. Gonadotropic function of the pituitary may be suppressed by the increase in other functions, i.e., growth; the gonads may be overstimulated with subsequent atrophy; the gonadotropic function of the pituitary, in turn, may be depressed by the increased outpouring of androgens.

Pituitary-gonadal reciprocities have been defined clearly from studies upon the effects of hypophysectomies of various experimental animals, as the result of the pioneer work of P. E. Smith. The effects of pituitary failure on the gonads and accessory sexual apparatus are illustrated best by the characteristic findings in hypophysectomized monkeys (5). In the testes of the adult hypophysectomized monkey only an occasional spermatogonium remains on the basement membrane. Indifferent or Sertoli-like cells make up the bulk of the seminiferous epithelium. The appearance becomes characteristic of that of prepubescence in the monkey and in the human male. Although the Leydig cells become functionally inactive, few striking cytologic alterations occur. Atrophic changes in the accessory sexual apparatus occur, however; these are of the same order as those which follow castration. From this description, it is evident that hypophysectomy or pituitary failure induces both germinal and endocrine failure of the testes.

Of the various pituitary syndromes, that of pituitary cachexia (Simmonds' disease) yields the most

striking degree of gonadal failure, one which is comparable to that observed following hypophysectomy. The other syndromes, such as pituitary dwarfism, adiposogenitalism, acromegaly and pituitary basophilism as well as those instances in which neoplasms about the pituitary interfere with its function, are characterized by various grades of gonadal failure, which involve both endocrine and germinal elements.

*Hypogonadism, due to diabetes mellitus.* Decreases in sexual potency, progressing at times to complete impotency and lowered fertility occur commonly in severe diabetics. Since these symptoms of hypogonadism are not always corrected by adequate dietetic measures and insulin therapy, they cannot be related in their entirety to the effects of the disturbed metabolism, malnutrition and cachexia produced by the disease. In the chronic cases, Koch (6) regards the cause of testicular impairment as circulatory in origin, due to the development of arteriosclerosis.

There is a surprising paucity of descriptions of sexual alterations in this condition. Warren (7) has observed no testicular alterations other than cessation of spermatogenesis and some increase in the thickness of the basement membrane of the tubules. He states that in the adequately treated patient there is no alteration from the usual testicular picture. Koch (6), however, has observed atrophy of the seminiferous tubules, followed in some instances by increase in interstitial tissue. Kyrle (8) describes the occurrence of testicular atrophy of the same order as seen in conjunction with severe metabolic disease, acute and chronic infections and diseases of the circulatory system. The fact that, under adequate therapy, normal gonadal function returns in many instances indicates the likely existence, prior to therapy, of a disturbed pituitary function secondary to metabolic and nutritional factors and the possible non-existence of any significant aberration in gonadal responsiveness. In the instance wherein hypogonadism continues despite adequate diabetic therapy, it seems reasonable to infer that circulatory alterations have produced intrinsic testicular damage of such degree as to render the testes unresponsive to normal pituitary influences.

*Hypogonadism due to adrenal disease.* In the hypocortical syndrome (Addison's disease), hypogonadism is common. Decreases in libido and lowering of fertility occur. Rowntree and Snell (9) and Grollman (10) describe the association of testicular atrophy with the disease. This involves both the germinal and the interstitial elements. The cause of this hypogonadism appears to be, most likely, a disturbance in pituitary function, secondary to the metabolic disturbances and the cachexia which characterize the disease. That no significant impairment of testicular

responsiveness necessarily follows is indicated by the fact that, during remissions of the disease, or as a result of therapy, adequate gonadal function may return.

*Hypogonadism due to causes primarily extra-endocrine in nature.* The most common of these are the debilitating effects of acute and chronic diseases, malnutrition and deficiency states. In these conditions, both endocrine and germinal impairment result from secondary alterations in the function of the pituitary. Any direct damage to the testes under these circumstances precludes their normal responsiveness if and when normal pituitary function returns.

As Reynolds and Macomber (11) observed, the testes become soft and decrease in size in malnutrition. Jaffé (12) reported that in chronic diseases the seminiferous tubules were separated by broad and mostly edematous connective tissue. Cordés (13) found spermatogenesis depressed in various acute diseases, he reported that the seminiferous tubules were thickened and the interstitial elements increased in malnutrition. Van Hansemann (14) was of the opinion that some increase in the interstitial cells occurs in all cachexias. Moore (3), however, has observed that these conditions, when severe enough to interfere with pituitary secretion, are always followed by low androgenic secretion. Simmonds (15) has observed that many chronic diseases may produce seminal failure without apparent alterations in the external appearance of the testes. Swelt and K'Ang (16) noted degeneration and hyalinization of the seminal epithelium and Bessey and Wolbrook (17) reported testicular atrophy in vitamin A deficiencies. Testicular atrophy and germinal impairment have been described in vitamin B deficiency. Parkes (18) related these to secondary alterations in the function of the pituitary. The striking effects of vitamin B deficiency in experimental animals, according to Mason (19), involve only the germinal epithelium and are associated with no androgenic deficiency. Jackson (20) has summarized the effects of inanition and malnutrition upon the testes in his general monograph on the subject.

Extreme sexual excesses may lead to hypogonadism. As an example of such excesses, Lepinasse (21) recalls the *Mujerados* of Mexico, whose sexual decadence was produced by artificial irritation. Consequent to the induced and almost continual spermatorrhea, marked testicular and genital atrophy occurred, associated frequently with loss of pubic hair and gynecomastia. In these instances, it is obvious that the subsequent hypogonadism is caused by direct testicular damage. Alterations, if any, occurring in the pituitary function are in the order of in-

creases. Exhaustion of the testes produces intrinsic refractivity to pituitary influences.

*Seminal failure of intrinsic gonadal origin due to failure of descent.* The thermo-sensitiveness of the seminiferous apparatus of the testes and its dependence for integrity of function upon the efficient scrotal thermo-regulatory function are well known. Ectopia of the testes resulting in inguinal or abdominal locations produces germinal impairment and, if it continues over long periods of time, interference with endocrine function; this may occur in cases classified in Group I, also. That these effects are direct testicular ones is obvious. If testicular impairment has not progressed too far, deposition of the testes into the scrotum is followed by a return of germinal and endocrine functions.

Felizet and Branca (quoted by Moore, 3) studied 51 cryptorchid testes. They found that the majority contained no cells of the germinal line. A few showed spermatogonia, but only two contained spermatids. None of the series had produced spermatozoa. Moore (3) has observed that, while the interstitial tissue of the cryptorchid testes secretes androgens, this secretion level may be lower than normal, an opinion which is shared by Korenchevsky (quoted by Moore, 3). Earlier opinions had been stated that often the amount of interstitial tissue was greater than normal and that there was an increase in the secretory activity of these elements. Many experimental data, as well as clinical observations, suggest that there results some endocrine impairment of the testes when the abdominal position is maintained over long periods of time. The studies of Hanes and Hooker (quoted by Moore, 3) upon the androgenic content of scrotal and cryptorchid hog testes bear out this belief.

*Seminal failure due to thyroid disease.* It is general clinical knowledge that impairment of thyroid function commonly results in disturbances of gonadal function. These thyrogonadal relationships have been studied more intensively in the female, in whom the gonadal manifestations of thyroid disease are more striking. In neither sex have any thoroughly acceptable experimental or clinical data regarding the *modus operandi* of these effects been accumulated. Salter (22) has suggested three possible types of thyrogonadal reciprocities, a), a 'peripheral sensitization' of tissues by the thyroid principle to gonadal hormones, b), effects produced by thyroid principle on the pituitary-gonadal axis, or vice versa, and c), indirect effects of the thyroid on the gonads by way of other glands, e.g., the adrenal. Moore (3) considered that thyroid effects upon the gonads were indirect and by virtue of the associated metabolic alterations. Van Dyke (1) has concluded that thyroid



secretion is probably of no great significance in the regulation of gonadal function, its usual effect, if any, being to lessen the action of the follicle-stimulating hormone. The experimental studies of Tyndale and Levin (23) suggested that this is a peripheral effect on the reactivity of the gonadal tissue rather than an effect on pituitary function. The observations of Howell (24) are difficult to reconcile with these views. This worker found increased gonadotropic titers in the urine of patients of both sexes with thyroid diseases, i.e., exophthalmic goiter, myxedema and adenomatous goiter. Our group (2) could find no direct effects of thyroid substance upon the pituitary-gonadal axis.

Meager, indeed, are any exact clinico-pathologic descriptions of the gonads in thyroid disease. General statements abound. Howard (25) observed that genital hypoplasia is not infrequent in hyperthyroidism but that no appreciable anatomic changes occur in the gonads. It may be assumed that the loss of libido and sterility in advanced hyperthyroidism may be due to the effect of the cachexia upon the pituitary function. The sexual-retarding effects of childhood hypothyroidism and cretinism are well known. Howard observed that complete impotence is the rule in cretins and quoted Langhans that the testes and epididymides of a 24-year-old cretin were of 'child-like size' and that spermatozoa were absent or markedly decreased in number. Clinical observations, however, indicate that sterility is not necessarily the rule with moderate or even severe hypothyroidism. Rolleston (26) has cautioned that men with myxedema are not necessarily sterile. Some of the best seminal specimens seen in our clinic were from men with low metabolic rates. Marañon (27) has reported the occurrence of left gynecomastia in two males with hyperthyroidism. There is good reason to believe that the primary gonadal effect of thyroid disease is peripheral and, for the most part, germinal in nature, the disturbed metabolism resulting in the formation of germinally inadequate spermatozoa.

*Seminal failure due to adrenal disease.* The significant effects of hyperplasia or tumors of the adrenal cortex upon the genital system are well known. The effects are produced by the outpouring of large amounts of androgens. In those cases arising before adolescence, which are those showing the most striking endocrine effects, spermatogenic function of the gonads fails to keep pace with the interstitial function. Germinal inadequacy is common in this condition, its cause probably being related to the depressing effect of the androgens upon pituitary gonadotropins.

Broster et al. (28) reported that their studies of the testes of 13 patients, who had developed adrenal

pathology during pre-adolescence, indicated the existence of spermatogenesis in only one case, whereas in 10 cases activity of the interstitial elements was observed. In the group of patients of pre-adolescent age, the testicular histology was not grossly abnormal, except that testicular tubules were less numerous than normal and there was some increase in the stroma. Spermatogenic epithelium appeared quiescent. Those patients of the group, however, who were of post-adolescent age showed a quite different picture. Spermatogenesis was inhibited, with resulting aspermia although the seminal epithelium did not necessarily show atrophy. There was a marked hyperplasia of the interstitial elements, the cells of which often formed large islets between the tubules.

*Seminal failure due to extra-endocrine causes.* These causes include the action of certain toxins and chemicals, febrile attacks and sexual excess. These effects are essentially local ones on the germinal epithelium without any or with minimal endocrine impairment. Certain toxins and various organic compounds and salts of heavy metals have depressing effects on spermatogenesis itself or on mature spermatozoa. Recently, sulfanilamide has been described as having depressing action on the seminal function (29). Alcohol is said to exert injurious effects on the germinal elements. Tobacco, too, may have harmful effects. Moore (3) has stated that prolonged febrile states are followed not infrequently by temporary sterility. Mills (30) found many instances in which the germinal epithelium was destroyed during attacks of epidemic pneumonia. Experimental studies on the rat (31), guinea pig (32), ram (33) and man (34) have indicated the extreme sensitivity of the spermatogenic apparatus to increased temperatures. On the other hand, spermatozoa are quite tolerant of low temperatures (35). Doubtless, the frequency of intercourse may play a rôle in seminal failure. What may be a normal and physiologic sexual regime for one individual may prove an exhausting drain upon the germinal epithelium of another. Desire for paternity, failure to achieve this desire and an increase in the number of sexual attempts are commonly observed to develop into a vicious circle leading to sexual exhaustion and seminal depletion.

#### DIAGNOSIS OF LEVELS OF GONADAL FUNCTION

This section must consider both the germinal and endocrine functions. The presence or absence of *libido sexualis* cannot be taken as proof of the non-existence or existence of hypogonadism. Rowe (36) wisely observed some years ago:

The chief clinical proponents of the theory of important endocrine activity of the testicle in adult years seem to

have adopted the existence of erectile power and the concomitant ability to indulge in intercourse as the principal if not the sole criterion of normal function. The well-known fact that castration in adult years, for a time at least, leaves the erectile power relatively unimpaired, is resolutely ignored as the only possible method of meeting so obvious a contradiction to their incretory doctrine

### Endocrine Levels

Diagnosis of hypogonadism (androgenic deficiency) must consider these objective data: size and consistency of gonads; anatomic state of penis and scrotum; condition of prostate and seminal vesicles; endocrine habitus, including voice, hair distribution and localization of fat, roentgenologic findings, especially epiphyseal status, anthropometric measurements, androgenic titers of urine, and blood chemistry studies, especially in regard to sodium, potassium and chloride metabolism (37)

Grave loss of androgenic function results in marked alterations in the accessory sexual organs, the severity of which is determined largely by the time in which the deficiency becomes apparent, i. e., whether it appears before or after puberty, and the resultant effects upon skeletal structure. The effects of a hypogonadism which occurs during pre-adolescent and adolescent years are grave. Due to retardation of epiphyseal closure, the individual usually grows tall and is slight of build. The lower measurement comes to exceed the upper and the span surpasses the height. Sexual maturation fails to occur. Axillary, pubic, limb, facial and trunk hair do not appear and the voice remains childlike. The external genitalia and prostate gland remain hypoplastic. Muscular growth is poorly defined, the small, flabby musculature suggesting feminine development. The skin is fine, smooth and boyish, but ages rapidly. Localized depositions of fat about the hips, pubes and breasts may be associated but more often are absent. Distinct personality changes are often manifested in the form of shyness, effeminate and retiring disposition and lack of aggressiveness and bodily strength. The basal metabolic levels may be depressed moderately to -20 or -25 per cent. Seminal failure is absolute.

The onset of marked androgenic failure of the testes after adolescence produces less striking changes. The various secondary sexual characteristics tend to regress but the skeletal structure is unaffected. The penis, scrotum and prostate become slightly smaller. The growth of hair on the face, chest, extremities, axilla and pubes may diminish but complete loss is usually not noted. Moderate elevation of the pitch of the voice may result. The *libido sexualis* may be diminished but is not wholly absent. Sexual ability is retained to some degree. Pronounced

decrease in the masculine aggressiveness, muscular strength and ambition results in the development of a rather placid individual. Vasomotor phenomena suggestive of the climacteric disturbances in women may occur.

The effects of moderate androgenic deficiency are determined likewise by the time of onset, i. e., whether before or after adolescence. Seminal failure is usually severe, erections being occasional in appearance, the seminal fluid scanty and containing few if any spermatozoa.

**Androgens** Studies of the urine of males with hypogonadism have been instituted with hopes that the detection of significant alterations in the levels of excretion of androgenic substances would permit a quantitative expression of the gonadal function. This hypothesis has not been supported by the clinical data available. The conflicting data may be reviewed briefly.

The studies of McCullagh, Cuyler and Frawley (38), McCullagh, McCullagh and Hicken (39), McCullagh and Renshaw (40), Kochakian (41) and Feiner and Rothman (42) disclosed no androgenic substances in the urine of male castrates. Later investigations, in which were employed improved methods of extraction and bioassay, by Peterson, Dorfman, Hansen (47), McCullagh and Callow (49) revealed varying amounts of androgenic substances in the urine of male castrates, the average of which was less than the values for normal men. Callow, Callow and Emmens (49) observed that the individual figures for their group of 11 castrates were within the range of variation for normal males. McCullagh and Lilga (50) studied the androgenic titers of 27 patients with hypogonadism, finding that the average values ranged from 0 to low normals. Their average for normal males had been found to be 37.8 i. u. daily. Five of their castrates excreted androgens varying from 0 to 18 i. u. daily. Kenyon, Gallagher, Peterson, Dorfman and Koch (45) observed that the excretion of androgens in their hypogonadal patients averaged about one-third of the values for their normal males (70 i. u. daily), similarly, two castrated males excreted 1 and 3.5 i. u., respectively, of androgenic substances per liter of urine. Similar results were reported by Hoskins, Coffman, Koch and Kenyon (51).

Data on normal individuals are variable. The studies of Talbot, Butler and MacLachlan (52) revealed that the daily excretion of total neutral 17 ketosteroids of children less than 7 years of age was 1.3 mg. but these values increased with age, attaining an average of 4.0 mg. for children between 7 and 12 years of age, and 8.2 mg. for children between 12 and 15 years of age. They observed that the average value of 17 ketosteroids for adult men (15.0 mg.) was slightly higher than that for adult women (10.2 mg.). Dingemans, Borchardt and Laqueur (53) have observed that boys before the age of puberty excrete 15 i. u. of androgenic substances per liter of urine whereas men

less than 40 years of age show individual variations from 15 to 170 I.U. of androgenic substances per liter of urine, averaging 40 to 50 I.U. per liter.

Qualitative variations in the nature of the androgenic materials recovered from urine have been reported. The studies of Callow (49, 54-56) indicate that the active androgenic substances, androsterone and dehydroisoandrosterone, as well as the inactive androgenic steroid, etiocholanol-3-( $\alpha$ )-17-one, are excretion products of androgenic metabolism found in the urine of both normal and castrated males. The ratio of androsterone to dehydroisoandrosterone in the urine of normal males has been reported to be 1:1 by Butenandt and associates (57-58), Callow and co-workers (49, 54-56, 59) and Dingemans and Laqueur (60). Employing the technique of capon assay and digitonin fractionation of the pooled urine specimens of two male castrates, which contained 6 I.U. of androgenic substances daily, Hoskins and Webster (61) observed that the ratio of androsterone to dehydroisoandrosterone was 4:1 as compared with the ratio of 1:1 reported above for normal urine. Hansen (47) suggests that the androgenic substance in the urine of male castrates resembles  $\Delta$ 4-androstenedione in its biological action, but Hoskins and Webster (61) attribute this property to the combined activities of androsterone and dehydroisoandrosterone rather than to any biological activity of excreted androstenedione. Callow and Callow (59) found a significant increase in the excretion of transdehydroandrosterone in one castrate, with slight depression of the urinary fractions of androsterone and etiocholanol-3-( $\alpha$ )-17-one. Inasmuch as Crooke and Callow (62) had previously reported an increased excretion of transdehydroandrosterone in the urine of patients with adrenal cortical tumors, this increase in the urinary fraction of transdehydroandrosterone in castrated males has been interpreted to indicate an extra-gonadal origin of the androgen, probably the adrenal cortex. Furthermore, Callow and colleagues (49) have suggested that the increased androgenic output from the adrenals may be compensatory for the absence of the gonads, the higher androgenic levels depressing the increased gonadotropic production of the pituitary; this is comparable to the observations of Hamblen, Ross, Cuyler, Baptist and Ashby (63) in climacteric women. The studies of Dorfman, Cook and Hamilton (64) and Dorfman and Hamilton (65) support the assumption that androgenic compounds may be gonadal or extra-gonadal in origin and that the reduction of testosterone to the various androgenic fractions excreted in the urine may occur in some site other than the testis.

Quantitative and qualitative studies of androgenic substances excreted in the urine of hypogonadal males do not permit the conclusion that diverse

grades of testicular failure may be diagnosed or quantified by androgenic determinations.

Estrogens, too, have been recovered from the urine of male castrates by Bingel (43), Eng (66), Hansen (47), Koch (44), Kenyon, Gallagher, Peterson, Dorfman and Koch (45) and Callow and co-workers (67). No comparisons of the estrogenic determinations of the various groups can be made inasmuch as the values for estrogens varied from one-third to 8 times the normal values within the same laboratories. Buxton and Westphal (68) and our group (69) have shown that the male is able to metabolize injected progesterone into the inactive excretion product, pregnenediol. Further studies of estrogenic metabolism in the normal male are necessary before clinical evaluation of alterations in the hypogonadal male is permitted.

### *Seminal Values*

The diagnosis of the level of seminal function may embrace three methods of study, a), complete examination of the seminal fluid, b), testicular or epididymal aspiration and c), testicular biopsy. The first of these studies is a routine part of every fertility survey. The latter two are indicated when azoospermia or marked decreases in seminal values are encountered. The seminal examination considers five factors: a), the volume of the seminal fluid; b), the number of spermatozoa; c), the degree of motility of the spermatozoa; d), determination of the relative percentage of normal and abnormal forms; and e), an estimation of the viability, i.e., the period of survival of the spermatozoa in seminal specimens.

*Volume.* The volume of the seminal fluid depends largely upon the quantity of secretion produced by the prostate and seminal vesicles rather than upon the concentration of the spermatozoa, clinical proof of which lies in the fact that post-gonorrheal bilateral epididymitis or bilateral vasectomy (70) produce no significant alterations in volume. Volume of the seminal fluid is increased by continence and decreased by excessive coitus, testicular atrophy, stenosis of the ejaculatory ducts and diseases of prostate and seminal vesicles. Experimentally, decreases in seminal volume have been produced by estrogenic therapy (71).

Depending chiefly on the period of continence, the volume varies considerably among normal men. Meaker (72) noted an average volume of 3 to 6 cc. after one week of continence. Pollák and Joél (73) observed the volume to vary from 3 to 5 cc. in normal men, with an average of 3.3 cc. following a period of continence for 4 to 7 days. Cary and Hotchkiss (74) established the lower limits of normal volume to be 3.5 cc. following a period of sexual rest of not less than 3 days. Hotchkiss, Brunner and Grenley (75) observed the average volume of semen for 200 fertile

men after 72 hours of continence to be 2.3 cc in condom specimens and 3.12 cc in withdrawal specimens. Weisman (76) recommends 5 to 7 days of continence and accepts a volume ranging from 2.5 to 5 cc as being within the normal range.

**Spermatozoal count** This affords considerable information concerning seminal function. In general, counts lower than 60,000,000 spermatozoa per cc or 150,000,000 in the total specimen indicate relatively lowered fertility. It should, however, be appreciated that the seminal count varies normally from time to time in the same individual, therefore, at least two seminal studies are advisable before an opinion concerning the numerical status of the spermatozoa can be formulated. Belding (77) enumerated some of the varied and obscure factors influencing the concentration and total number of spermatozoa as follows: Age, frequency of sexual intercourse, relative abundance of prostatic secretion, season, exercise, diet, mental strain, fatigue, functional adequacy of the endocrine glands and debilitating diseases.

Considerable difference of opinion exists as to the lower numerical limits of fertility. Meaker (72) states that no pregnancies have occurred in his cases in which the total spermatozoal count was less than 60,000,000. Hotchkiss (78) noted a few exceptions in patients with total counts of less than 60,000,000. He reported the average count for fertile males to be 100,000,000 to 150,000,000 per cc or 400,000,000 to 500,000,000 in the total specimen. Macomber and Saunders (79) observed that the average count for 277 normal and abnormal individuals was 100,000,000 per cc. Hotchkiss, Brunner and Grenley (75) found the average count in 200 fertile men to be 120,630,000 spermatozoa per cc and 346,020,000 for the total ejaculate. Belding (77) reported 119,000,000 spermatozoa per cc for a series of fertile matings and 70,000,000 per cc for a group of sterile matings. Pollak and Joel (73) considered the normal variation ranges from 60,000,000 to 120,000,000 spermatozoa per cc. Discrepancies in the accuracy of spermatozoal counts may be attributed to a personal error of 10 per cent in either direction, in addition to errors in sampling semen, dilution of the fluid, and the method used (76).

Hamblen (80), citing the error of accepting any strict criteria for seminal normality, has reported interesting data regarding the seminal findings in husbands of barren couples eventually attaining parenthood, the studies reported being those closest related temporally to the occurrence of pregnancies. The average composite values for the seminal fluid of the group were, a), volume, 4 cc, b), abnormal forms, 37 per cent, c), motility, 58 per cent, and d), count 101,000,000. The range of values for individual specimens was as follows:

|                              |                          |
|------------------------------|--------------------------|
| Volume                       | 1 to 8 cc                |
| Abnormal forms               | 14 to 67 per cent        |
| Motility                     | 8 to 95 per cent         |
| Number of spermatozoa per cc | 2,000,000 to 249,000,000 |

**Motility** Numerous observers believe the optimum degree of motility of spermatozoa to be above 80 per cent, although Cary and Hotchkiss (74) have observed a state of relative fertility in their patients manifesting spermatozoal motility as low as 25 per cent. Weisman (76) has pointed out, however, that seminal specimens should not be examined earlier than 45 minutes, in order to permit liquefaction to take place, or later than 3 hours.

More attention should be paid, perhaps, to the kind of motion exhibited by spermatozoa rather than being satisfied with the fact that they are motile. Five kinds of motions have been described (72), a), progressive vibratile, b), undulatory tactile, c), stationary bunting, d), rotary swimming, and e), pendulum swimming. The latter two kinds of motion have been considered abnormal.

Decreased motility (76) may be the result of either external or internal factors. The external factors include a), various contaminants in the receptacle, such as spermocidal chemicals, b), extreme heat, or c), tap water (81). The internal causes include a), sexual exhaustion with resultant formation of immature spermatozoa, b), various lesions of the genito-urinary tract ascribable to gonorrheal infection, orchitis following mumps, and c), toxic depression of the germinal epithelium by chemical factors, such as drugs and metals (76). Charny (70) stresses that necrozoospermia is usually associated with oligozoospermia and poikilozoospermia. The finding of necrozoospermia alone, according to Charny, focuses attention upon the toxic adnexal secretions rather than endocrine failure of the testes.

**Spermatozoal morphology** This is considered by most investigators to offer the greatest amount of information concerning germinal adequacy. Meaker (72) has observed that the abnormal forms are less than 15 per cent in highly fertile men but as high or higher than 40 per cent in individuals of lowered fertility. The studies of Moench (82) revealed that the abnormal forms in fertile men rarely exceeded 20 per cent and that, if a higher percentage of abnormal spermatozoa existed, sterility and abortion followed commonly. It is accepted generally that the presence of excess numbers of abnormal spermatozoa represents defective spermatogenesis.

Abnormal forms represent, in general, spermatozoa which do not conform to the general appearance of average spermatozoa. The abnormalities of morphology may be manifest in the head, the body or the tail. In general, abnormal forms may represent immature spermatozoa, characterized by an excessive

amount of cytoplasm around the head or body and usually a rudimentary tail (70), or degenerated spermatozoa, in which alterations of structure are so numerous as to defy description.

**Spermatozoal viability.** Although it is agreed generally that a definite attribute of healthy spermatozoa is the ability to remain motile for considerable time at an optimum temperature, the significance of asthenozoö spermia, other than confirmatory evidence of pathologic spermatogenesis, remains obscure.

Considerable variation in statements concerning the viability of normal spermatozoa exist. Cary and Hotchkiss (74) believe spermatozoal activity should be present at the end of 5 or 6 hours. Belding (83) states that the majority of spermatozoa may endure at room temperature for 30 to 32 hours and at body temperature for 23 hours. Moench (84) observed that most spermatozoa maintained at body temperature for 18 hours died. Meaker (72) reported a case in which pregnancy occurred from spermatozoa the viability of which did not exceed 8 hours. Weisman (85) concludes that spermatozoa that do not endure incubation at 37.5° C. for at least 12 hours or survive at room temperature for 24 hours may be considered pathologic.

When severe seminal impairment is indicated by seminal analysis, histologic studies of the germinal epithelium secured by testicular biopsy affords considerable information concerning the functional activity of the seminiferous tubules. In this manner obstructive lesions along the ducts of egress of the spermatozoa may be differentiated from primary failure of the germinal elements.

#### SUMMARY

When a diagnosis of hypogonadism or seminal failure without androgenic failure has been established, search must then be made for the various etiologic factors responsible for these gonadal alterations before the prognosis may be determined or rational therapy be instituted. The segregation of the various causative factors is not always easy. Testing with either stimulating or substitution endocrine substances may form a part of the diagnostic effort.

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# Clinical Determination of Pregnanediol Excretion

[A Review Article]

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PREGNANEDIOL was one of the earliest of the sex steroids to be isolated from human pregnancy urine (1) and characterized (2). It was found to be physiologically inert, and was ignored by biologists and clinicians for several years. To the steroid chemists it was of interest as a possible inactive excretion product of an active precursor. Butenandt, in 1934 (3), oxidized pregnanediol to progesterone. This not only showed the close chemical relationship between the two steroids, but was the first synthesis *in vitro* of the active principle of the corpus luteum.

Demonstration of the biological relationship between pregnanediol and progesterone, as well as the correlation of the level of corpus luteum activity with the excretion of pregnanediol had to await a semi-quantitative, semi-micro method for the determination of pregnanediol. Venning and Browne did the preliminary work for this with their isolation, in 1936, of a water-soluble pregnanediol complex from human pregnancy urine (4). Venning later modified the isolation procedure slightly to give a method applicable to the routine determination of small amounts of sodium pregnanediol glucuronide, one of the excretory forms of this steroid.

That this method filled a manifest need is apparent from the work that has been reported in which it was employed. The information obtained from its use by the originators and other investigators can be briefly summarized as follows. From 10 to 30 per cent of administered progesterone can be recovered from the urine as sodium pregnanediol glucuronide. In the course of a normal menstrual cycle from 3 to 50 mg. of pregnanediol can be isolated, this excretion starting soon after ovulation and the formation of the corpus luteum, rising to a maximum about one week before the next bleeding, and falling off to zero before flow starts. In a normal pregnancy, excretion of pregnanediol remains at the level characteristic of the menstrual cycle for about 8 weeks, then rises until it reaches 100 to 150 mg. per diem by the 38th week, and falls off until the initiation of labor. In cases of menstrual irregularities, complicated preg-

nancies, or, in common with the other urinary sex steroids, hepatic or renal dysfunction, the excretion will be altered, usually to a lower level.

A multiplicity of methods confronts the investigator who wishes to determine the level or presence of corpus luteum activity. The most direct evidence of corpus luteum function is the well-developed progestational change in the endometrium. Samples of this tissue may be obtained for examination by either curettage or biopsy. Neither of these procedures can be repeated too frequently. Furthermore, the information they give is qualitative in nature, making it difficult to determine the level of activity. More quantitative information can be obtained from the determination of pregnanediol excretion.

The most widely used method for determining this is the classical one of Venning (5). The glucuronide is extracted from the urine by shaking several times with butanol. After evaporation of the solution *in vacuo*, and re-dissolving the residue in alkali solution, the complex is precipitated with acetone. The precipitate, after final purification, is determined by weighing, and identified by its melting point and mixed melting point with a known pure sample.

There are two major disadvantages to this method, which have been responsible for two major developments in the analysis. One of these is the difficulty of checking the identity and purity of the final precipitate. All too frequently specimens of urine obtained during the luteal phase of a cycle will yield amorphous precipitates of less than 5 mg. Amorphous compounds have no fixed melting points, so that their identification by this method is unsatisfactory and inconclusive. This difficulty has led to work on the determination of the glyconuronic acid content of the precipitate (6, 7). These procedures determine the reducing activity of the precipitate before and after hydrolysis, measuring this with an alkaline copper reagent either colorimetrically or titrimetrically. If the Venning method is used, some such form of glycuronic acid analysis should be employed to check small and dubious precipitates. The colorimetric method of Maughan, Evelyn and Browne (8) for the direct determination of glycuronic acid or sodium

pregnanediol glucuronide, by condensation with aqueous naphthoresorcinol may also be employed.

The other major disadvantage is inherent in the determination of pregnanediol as its glucuronide. It is not definitely known, as yet, whether all pregnanediol excreted is conjugated with glycuronic acid. More troublesome, practically, is the instability of the conjugated glucuronide, which hydrolyzes readily at room temperature. This characteristic necessitates special care in chilling the specimen immediately after voiding, and analyzing the urine within 15 hours of collection (9). Since it is the complex that is determined, hydrolysis will cause the results to be low or negative. Technically, extraction by shaking with butanol is tedious, design of a continuous extractor to handle this solvent is difficult, since butanol is particularly prone to form emulsions with urine.

Two radically new methods overcome these difficulties. They employ simplified extraction procedures, and determine the relatively rugged molecule of pregnanediol instead of its fragile complex. One of these is the method of Astwood and Jones (10) which combines hydrolysis with extraction by refluxing the acidified urine with toluene. After purification and evaporation of the toluene extract, the steroid is dissolved in ethanol and precipitated from this solution with alkali. This precipitate is recrystallized, transferred to ethanol, and the solution evaporated and weighed. Purity of the precipitate is checked by its melting point.

A modification of this method is that of Talbot, Berman, MacLachlan and Wolfe (11), which is especially useful when a 17 ketosteroid determination is to be made on the same specimen. The urine specimen is hydrolyzed and extracted with any steroid solvent in a continuous extractor designed for it. The crude neutral fraction of the extract is treated with Guard's Reagent "T" which separates the ketonic and non-ketonic fractions by reacting with ketone groups to give water soluble compounds. A toluene solution of the water insoluble, non ketonic fraction of the extract, which contains the pregnanediol, is purified by the method of Astwood and Jones. Final assay is made either gravimetrically or colorimetrically by treating the steroid with sulfuric acid. This is a Salkowski reaction, and is the simplest of the general steroid color reactions, addition of acetic anhydride to this makes it the Lieberman reaction which is

commonly used for the determination of cholesterol. The use of one of the non-specific steroid color reactions on a precipitate which, by reason of the isolation procedure, contains chiefly pregnanediol is at least as accurate as weighing a precipitate of indeterminate composition, and may prove more rapid for routine use, as well as indicating the steroid content of the precipitate.

Methods of determining pregnanediol are, at present, in a state of flux. Those who are among 'the last to cast the old aside' will continue to use the Venning method. With extreme care in collection and handling of the urine, this method, with ancillary glycuronic acid analysis, even though cumbersome and ill-adapted to routine use, will give results which are unlikely to be questioned. 'The first by whom the new is tried' will find that the newer procedures which determine the molecule as a steroid, and not as a glucuronide, as far more flexible and better adapted to routine use.

The ideal clinical method for determining pregnanediol has yet to be published. It must be adapted to routine use, since the number of cases of menstrual irregularity encountered in clinical endocrinology is large, and the determinations needed for each patient are many. The compound chosen for analysis should be stable in order to make routine collection practical for outpatients. The method should be sensitive to at least a milligram, and accurate to half of that. The terminal reaction should be unique for pregnanediol, so that the pregnanediol content of the precipitate will be known.

All of the methods mentioned above have some of these features, none has all of them.

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# Disposal of Glucose at High and Normal<sup>1</sup> Blood Sugar Levels under Action of Insulin

[Diabetes Mellitus]

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IT IS OF PRACTICAL IMPORTANCE in the treatment of diabetic patients to know if there is a difference in the rate of disappearance of glucose under the action of insulin at different blood-sugar levels. Our interest in this problem was aroused during routine observations on diabetic patients. We observed a patient on insulin with the blood sugar in the normal range who did not excrete the extra glucose ingested when placed on a high carbohydrate diet with the same insulin dose. The latter regime was associated with a high blood-sugar level and the result was similar to that which has been reported by others (1, 2, 3).

This paper summarizes the results of a study of the disposal of glucose at normal and high blood-sugar levels under the action of the same amount of insulin. The study was made on depancreatized animals as well as diabetic patients.

## METHODS

The scheme of experiment employed in the diabetic patients and the depancreatized dog and rabbit were essentially the same. At least two series of observations were made in each case, *a*) with the blood sugar kept within the normal range for 3 to 6 hours with a given dose of insulin and *b*), with the blood sugar maintained at a high level (300–600 mg. per cent) for 3 to 6 hours with the same dose of insulin. Glucose in physiological saline was given as a constant intravenous drip with the amount required per hour to maintain the desired blood-sugar level regulated by frequent blood-sugar determinations. The total urinary sugar output was measured in all cases. The animals were catheterized and the bladder washed out at the beginning and end of the test

periods. As the interval during which the blood sugar was maintained at a constant level did not always correspond exactly with the times of catheterization, or in the case of patients, urination, the amount of sugar excreted in the urine was adjusted to the blood-sugar periods.

Blood-sugar determinations were made on venous blood by the micro Folin-Wu method. Urine sugar was determined by the quantitative Benedict method. Glycogen determinations were performed by the Pflüger method. Nembutal anesthesia was used in the animal experiments.

The diabetic patients used had no serious complications and were in good condition and the diabetes was under control at the time of study.

When the blood-glucose concentration is not kept relatively constant in balance studies of glucose utilization, elaborate calculations are necessary to compute the amount of sugar in the body fluid. Various workers use different figures for the amount of interstitial fluid; and, more important, the glucose balance between interstitial and intracellular fluid is uncertain. Since corrections are always open to question, an attempt was always made to keep a relatively constant blood-sugar level. At the high blood-sugar levels this ideal was not always obtained. However, if the blood-sugar level was lower at the end of a test than at the beginning, it is obvious that more glucose could have been disposed of than the amount tabulated and corrections are not essential in such cases. As will be evident from our results this constitutes an *a fortiori* argument in favor of our conclusions.

## RESULTS

*Patients.* The results obtained on 4 diabetic patients are summarized in table 1. Figures 1 and 2

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<sup>1</sup> Normal blood sugar is used to indicate a blood-sugar level within the physiological range (80–140 mg. %).

TABLE 1 GLUCOSE DISPOSAL AT HIGH AND NORMAL BLOOD-SUGAR LEVELS IN DIABETIC PATIENTS<sup>1</sup>

| Patients   | Duration of Experiment       | Regular Insulin Subcut., u | Blood Sugar Levels, mg % |                | Glucose Intravenously, gm | Glucose in Urine, <sup>2</sup> gm | Glucose Retained, gm |
|--|------------------------------|----------------------------|--------------------------|----------------|---------------------------|-----------------------------------|----------------------|
|  |                              |                            | Initial                  | Final          |                           |                                   |                      |
| 1. A S male 57, diet C 175, P 70, F <sup>3</sup> 80<br>R I <sup>4</sup> 10-10-5    | 5 hr. 47 min<br>5 hr. 40 min | 10<br>15 <sup>5</sup>      | 592 4<br>120 5           | 482 0<br>125 0 | 255 0<br>38 2             | 106 00<br>0                       | 149 00<br>38 20      |
| 2. N S female, 14, diet C 150, P 65, F 80<br>C I <sup>6</sup> 30-20-20             | 6 hr.<br>5 hr. 30 min        | 20 C I<br>20 C I           | 540 0<br>142 8           | 430 0<br>129 8 | 249 5<br>52 78            | 98 00<br>3 67                     | 151 50<br>49 11      |
| 3. S J, female, 13, diet C 200, P 75, F 80<br>R I 15-0-10<br>P Z I <sup>7</sup> 30 | 4 hr 46 min<br>4 hr          | 10<br>10                   | 452 0<br>81 3            | 384 0<br>85 1  | 178 0<br>34 9             | 48 20<br>0                        | 129 80<br>34 90      |
| 4. F F, male, 36, diet C 175, P 70 F 80<br>Insulin 25-10-25-10                     | 4 hr<br>6 hr 4 min           | 10<br>10                   | 551 6<br>140 8           | 551 6<br>149 2 | 217 9<br>57 0             | 82 00<br>1 50                     | 135 90<br>55 50      |

<sup>1</sup> Patients fasting throughout test<sup>2</sup> Aliquot samples on urine<sup>3</sup> C, Carbohydrate, P, Protein, F, Fat<sup>4</sup> R I, regular insulin<sup>5</sup> 10 U 6.40 A M } Test started 8 30 A M  
5 U 9 05 A M }<sup>6</sup> C I, crystalline insulin<sup>7</sup> P Z I, protamine zinc insulin.

show the record of one patient (patient S J, number 3, table 1) in detail to illustrate how the results tabulated in table 1 were obtained. The time period included in the graphs is longer than that given in the tables since the period used in the tables was made between two points where the initial and final blood-sugar levels were approximately the same. The graphs show a longer period since they include the time required to bring the blood sugar to the normal level in one instance and to raise it to a high level in the other. A striking increase in glucose disposal at high blood sugar levels occurred. Three and 7 times as much sugar disappeared under the action of insulin at the high blood sugar level in patient S J as at the normal level. This figure varied from 2.4 to 3.7 for different patients. The patients included two moderately severe juvenile diabetics and two milder, older diabetics.

**Depancreatized animals** The results on 4 depancreatized dogs are summarized in table 2. Figures 3 and 4 are the detailed study of one dog (dog D, number 3, table 2) and illustrate the method by which the results in table 2 were obtained (A slightly longer time period was included in the graphs than in the table as explained above). In 3 dogs, 1.6 to 2.6 times as much glucose disappeared under the action of insulin at the high blood sugar level as at the normal level. The utilization rate calculated as grams of glucose retained per kilogram per hour showed a marked difference between the high and normal blood sugar level. At the high blood sugar level with insulin the rate varied in the different dogs from 0.60 gm per kg per hour to 2.63 gm per kg per hour, with an average of 1.20 gm per kg per hour. At the normal blood sugar level the rate varied from 0.25 gm to 0.76 gm, with an average of 0.52 gm, per kg per hour. In one dog (dog S, number 2, table 2) there was

no difference in glucose disposal at high and normal levels. As this dog died it was not possible to check the determinations. Duplicate runs at both high and normal levels with insulin were made in dog D (table 2) with a difference of less than 8 gm between the

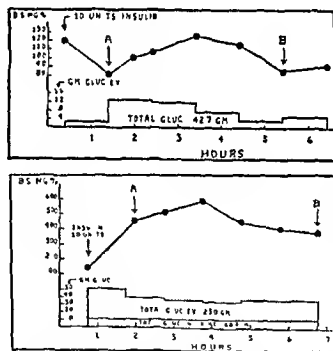


FIG. 1, (upper) DISPOSAL OF GLUCOSE AT A NORMAL BLOOD SUGAR LEVEL WITH INSULIN IN PATIENT S J. Patient fasting throughout test. No sugar in urine. Arrows A and B indicate period of test used in calculation of glucose disposal as recorded in table 1 (see text). Abbreviations: B S, blood sugar; Gluc, glucose; I V, intravenous. FIG. 2, (lower) DISPOSAL OF GLUCOSE AT A HIGH BLOOD-SUGAR LEVEL WITH INSULIN IN PATIENT S J. Arrows A and B indicate period of test used in calculation of glucose disposal as recorded in table 1 (see text).

determinations for the normal level and 3 gm at the high level.

The results on 4 depancreatized rabbits are tabulated in table 3. In many respects these results were unsatisfactory. Large amounts of insulin were required in these animals, due to a phase of relative insulin resistance. Also, it was difficult to prevent

TABLE 2. GLUCOSE DISPOSAL AT HIGH AND NORMAL BLOOD-SUGAR LEVELS IN DEPANCREATIZED DOGS<sup>1</sup>

| Dog     | Weight<br>kg. | Duration of<br>Experiment                | Regular<br>Insulin,<br>I.V. <sup>2</sup><br>u | Blood-Sugar<br>Levels, mg % |             | Glucose<br>I.V.,<br>gm. | Glucose<br>in Urine,<br>gm. <sup>3</sup> | Glucose<br>Retained,<br>gm. | Glucose<br>Utilized,<br>kg. gm./hr. |
|---------|---------------|--|---|-----------------------------|-------------|-------------------------|--|-----------------------------|-------------------------------------|
|         |               |  |   | Initial                     | Final       |                         |  |                             |                                     |
| 1, R    | ?             | 4 hr., 56 min.<br>5 hr. 53 min.          | 10<br>10                                      | 380                         | 296         | 68.90                   | 19.80                                    | 49.10                       | ?                                   |
|         |               |  |   | 221                         | 250         | 30.25                   | 0.60                                     | 29.65                       |                                     |
| 2, S    | 9.9<br>10.4   | 6 hr., 8 min.<br>7 hr., 5 min.           | 10<br>10                                      | 500                         | 472         | 72.47                   | 56.50                                    | 15.97                       | 0.26                                |
|         |               |  |   | 125                         | 122         | 18.50                   | 0  | 18.50                       |                                     |
| 3, D    | 6.7           | 4 hr., 48 min.                           | 10  | 412                         | 380         | 59.70                   | 14.70                                    | 45.00                       | 1.40                                |
|         | 6.8           | 5 hr., 56 min.                           | 10  | 570                         | 433.3       | 69.17                   | 26.20                                    | 42.97                       | 1.06                                |
|         | 6.5           | 6 hr., 55 min.                           | 12  | 75                          | 88          | 19.90                   | 0  | 19.90                       | 0.43                                |
|         | 8.2           | 5 hr., 32 min.                           | 10  | 77                          | 82          | 27.50                   | 0  | 27.50                       | 0.60                                |
|         |               |  |   |                             |             |                         |  |                             |                                     |
| 4, C    | 5.45          | 4 hr., 23 min.                           | 0   | 457                         | 420         | 27.80                   | 21.40                                    | 6.40                        | 0.31                                |
|         | 5.22          | 4 hr., 3 min.                            | 10  | 534                         | 500         | 45.00                   | 19.40                                    | 25.60                       | 1.62                                |
|         | 5.22          | 4 hr.                                    | 10  | 154                         | 156         | 15.80                   | 0.37                                     | 15.43                       | 0.76                                |
|         | 4.25          | 6 hr. <sup>4</sup><br>3 hr. <sup>4</sup> | 30<br>20                                      | 74<br>381                   | 66.5<br>384 | 13.10<br>41.80          | 0.39<br>8.13                             | 12.71<br>33.67              | 0.50<br>2.63                        |
|         |               |  |   |                             |             |                         |  |                             |                                     |
| 5, N.D. | 8.57          | 4 hr., 30 min.                           | 20  | 500                         | 512         | 40.60                   | 16.80                                    | 23.80                       | 0.60                                |

<sup>1</sup> Dogs fasting throughout test.

<sup>2</sup> I.V.—intravenously.

<sup>3</sup> Aliquot samples on urine.

<sup>4</sup> Tests run same day in sequence.

some wide fluctuations of the blood sugar. A definite difference, however, in glucose disposal at high and normal blood-sugar levels is seen with increased glucose disposal at high blood sugar levels.

DISCUSSION

It is obvious from the results tabulated here that far more glucose disappeared at high blood-sugar

levels than at the normal level with the same amount of insulin. The results given all represent glucose disposal under the action of insulin. Soskin (4) has reported glucose disposal rates in the acutely eviscerated animal at high blood-sugar levels but without insulin. He gives a utilization rate of 410 mg. of glucose per kg. per hour with a blood-sugar level of 285 mg. per cent. This is a lower rate than we obtained with high blood-sugar levels in depancreatized dogs with insulin in which the average rate was 1200 mg. per kg. per hour. In one dog (dog C, No. 4, table 2) which was observed at a high blood-sugar level both with and without insulin the utilization rate was 0.3 gm. without insulin, contrasted with 1.62 to 2.63 gm. per hour with insulin.

The mechanism and site of action of the increased disposal of glucose at high blood-sugar levels in comparison with normal levels with the same dose of insulin is not clear. In patients an increased secretion of endogenous insulin may account for increased glucose disposal at high blood-sugar levels. This could hardly be the major mechanism, for similar results were obtained in completely depancreatized animals although the percentage increase in glucose disposal at high blood-sugar levels was less than in the diabetic patients. De Nayer et al. (5) believe that the liver is the organ that disposes of glucose under insulin action in the normal blood-sugar range. They found that the normal dog with the maximal insulin effect disposed of 1.30 gm. of glucose per kg. while the hepatectomized animal utilized only 0.35 gm. of glucose per kg. whether with or without insulin. Whether this is true at high blood-sugar levels has not been determined.

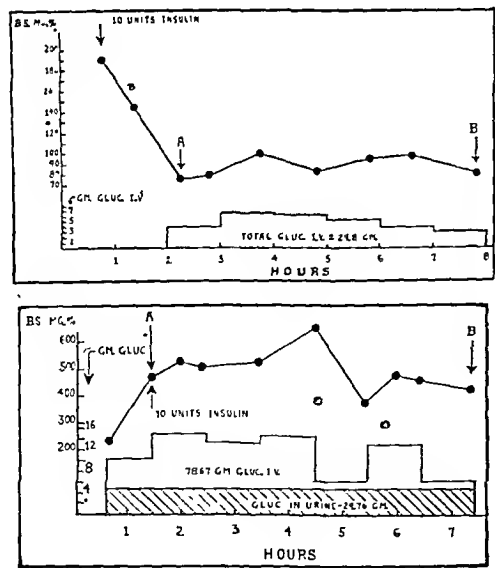


FIG. 3, (upper). DISPOSAL OF GLUCOSE AT A NORMAL BLOOD-SUGAR LEVEL WITH INSULIN IN DEPANCREATIZED DOG D. Depancreatized dog 3 (table 2), weight 8.2 kg.; dog fasting throughout test. No sugar in urine. Arrows A and B indicate period of test used in calculation of glucose disposal as recorded in table 2 (see text). FIG. 4, (lower). DISPOSAL OF GLUCOSE AT A HIGH BLOOD-SUGAR LEVEL WITH INSULIN IN DEPANCREATIZED DOG D. Depancreatized dog 3 (table 2), weight 6.8 kg. Dog fasting throughout test. Arrows A and B indicate period of test used in calculation of glucose disposal as recorded in table 2 (see text).

Cori and Cori (6) accounted for 95 per cent of the glucose given to rats with 15 u of insulin and a blood-sugar level of 77 mg per cent by oxidation or glycogen storage in a test period of 4 hours. Best, Hoet, and Marks (7) in the eviscerated spinal cat also accounted for most of the glucose given with 30 u of insulin and a blood sugar level between 440 and 510 mg per cent over a period of 3.5 hours by glycogen increase and oxidation. In contrast to this previous work we are unable to account completely for the glucose disposed of at high blood sugar levels by glycogen increase in liver and muscle and by oxidation.

glycogen of two depancreatized dogs and one depancreatized rabbit actually decreased at high blood-sugar levels with insulin. This is in distinct contrast to the idea which is prevalent that there is an increase in liver glycogen with insulin action at high blood-sugar levels.

The study reported here is of practical importance in the clinical control of diabetes. It should be recognized by those using insulin that the ingestion of additional carbohydrate leading to a high blood sugar level with the insulin kept the same does not lead to the excretion of all of this extra carbohydrate. When

TABLE 3. GLUCOSE DISPOSAL AT HIGH AND NORMAL BLOOD-SUGAR LEVELS IN DEPANCREATIZED RABBITS<sup>1</sup>

| Rabbit | Weight<br>kg | Duration<br>of Experiment | Regular<br>Insulin<br>I V,<br>u | Blood Sugar<br>Levels, mg % |       | Glucose<br>I V,<br>gm | Gluc <sup>2</sup><br>in Urine,<br>gm | Gluc<br>Returned<br>gm | Glycogen, <sup>3</sup> gm |       |         |       |
|--------|--------------|---------------------------|---------------------------------|-----------------------------|-------|-----------------------|--------------------------------------|------------------------|---------------------------|-------|---------|-------|
|        |              |                           |                                 |                             |       |                       |                                      |                        | Liver                     |       | Muscle  |       |
|        |              |                           |                                 | Initial                     | Final |                       |                                      |                        | Initial                   | Final | Initial | Final |
| 1      | 1.5          | 6 hr 17 min               | 30                              | 317                         | 326   | 7.85                  | 4.38                                 | 3.47                   | 2.47                      | 2.78  | 0.08    | 0.18  |
| 2      | 1.73         | 4 hr 11 min               | 30                              | 534                         | 500   | 5.85                  | 3.38                                 | 2.47                   | 0.12                      | 0.65  | 0.23    | 0.47  |
| 3      | 1.82         | 4 hr 28 min               | 30                              | 364                         | 303   | 7.65                  | 1.41                                 | 6.24                   | 1.13                      | 0.75  | 0.1     | 0.15  |
| 4      | 0.97         | 1 hr 25 min               | 60                              | 75.5                        | 84    | 0.72                  | 0                                    | 0.72                   | 0.31                      | 0.72  | 0.11    | 0.05  |

<sup>1</sup> Rabbits fasted 1-2 days before test and during test.

<sup>2</sup> Aliquot samples on urines.

<sup>3</sup> Slight difference in time factor on biopsies and blood sugar levels.

In dog ND (table 2) the muscle glycogen decreased from 0.32 to 0.27 per cent during 4.5 hours with a blood-sugar level between 500 and 512 mg per cent. In dog C, weight 4.25 kg. (table 2), 33.67 gm of glucose was disposed of under the action of insulin at a high blood sugar level. Only 10.3 gm of this could be accounted for as increased muscle glycogen (muscle glycogen increase was 0.46 per cent.). The liver glycogen decreased during the same period from 5.03 to 4.55 per cent.

In one depancreatized dog ND (table 2) oxygen consumption was measured twice during the test with elevated blood sugar. In each instance the oxygen consumption was 2.48 liters per hour or 11.16 liters for the 4.5 hour test period. The 23.8 gm of glucose utilized would have required 17.78 liters of oxygen (1 gm of glucose is oxidized by 747 cc. of oxygen). As noted above there was a decrease in both liver and muscle glycogen during the same period in this dog.

In the depancreatized rabbits similar results were obtained. The glucose which disappeared could not be accounted for by liver or muscle glycogen increase (table 3). The fate of this glucose, which cannot be accounted for in balance studies, is not known. Possibilities which should be explored are conversion to other intermediary carbohydrate compounds or to fat.

We were impressed with the fact that the liver

insulin action and carbohydrate are not balanced at high blood sugar levels due to excess carbohydrate; there is a compensating mechanism which acts usefully to dispose of more glucose. This fact re-emphasizes the futility of simple insulin-carbohydrate ratios. These ratios differ from patient to patient and, as we have shown here, vary in the same patient with changing blood sugar levels, the ratio increasing at the higher levels.

#### CONCLUSIONS

1. In 4 diabetic patients, 3 depancreatized dogs and 3 depancreatized rabbits more glucose disappeared under the action of insulin at a high blood-sugar level than at the normal physiological level. The fact should be stressed that this difference occurred with insulin and possibly may not occur without insulin.

2. The glucose which disappeared at high blood-sugar levels with insulin could not be fully accounted for by increased liver or muscle glycogen or by oxidation. The liver glycogen in the depancreatized animals actually dropped at the high blood sugar levels.

3. These results are of importance clinically since they show that there is not a strict overflow mechanism at high blood sugar levels with insulin because of an increased insulin-carbohydrate ratio at such levels.

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# Insulin Allergy

## A Report of Eight Cases with Generalized Symptoms

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THE PROBLEM OF INSULIN ALLERGY has been discussed by Tuft (1), Allen and Scherer (2), Herzstein and Pollack (3), McDaniel (4), and among others and most recently by Harten and Walzer (5) and by Yasuna (6).

**Definition.** The terms insulin sensitivity and hypersensitivity have been used frequently as synonyms for allergy, but they also have been applied to describe the rapid and excessive hypoglycemic response to insulin in contradistinction to insulin resistance or insensitivity. In this sense, sensitivity differs from allergy completely, not only in symptomatology but also in its mechanism. It may occur with or without allergic symptoms. An attempt should be made, therefore, to differentiate these two conditions in their terminology. In this paper we propose to use the term 'allergie' as referring to symptoms which are due to the antigenic property of insulin as a protein substance (7) and to speak of sensitivity and insensitivity as referring to the varying degrees of body response to the specific metabolic function of insulin as a hormone.

**Symptomatology.** About 20 per cent of all persons treated with insulin have been reported to show mild and transient local allergic reactions (2, 4, 5). Within a week or 10 days after the beginning of treatment swelling and erythema which persist for 30 minutes to several hours will occur at the site of injection. Itching and induration may be present. Usually these reactions will not interfere with the action of insulin as such and they will disappear without special care after a period of 10 days or 2 weeks. Sometimes changing the brand of insulin may be helpful.

In a few patients, however, the local reactions increase in severity, extend in size and spread over the body causing generalized urticaria with involvement of the mucous membranes, with severe pruritus, joint pain, headaches, elevated temperature, and circula-

tory and gastro-intestinal symptoms. These reactions usually develop slowly over a period of several hours and may persist for more than one day. They do not subside spontaneously with the continued use of insulin, but require desensitization or the cessation of insulin treatment.

These generalized allergic reactions after insulin are rare. Harten and Walzer (5) have found about 200 case reports in the world literature between 1923 and 1940 but in many of these there was insufficient evidence that the characteristic symptoms were due to the insulin protein itself rather than to non-specific animal proteins, pancreas extract or preservatives present in the insulin preparations. Yasuna (6) in his critical review accepted only 11 cases from the literature as proven generalized insulin allergy and added one case of his own. In the meantime 3 more cases have been reported, 2 by Herzog (8) and one by Hinko, Fenton and Balberor (9). Satisfactory immunologic tests have been possible only since crystalline insulin has become available. Cannon and Marshall (10) have described a new insulin-precipitation test which will be of help, in addition to the commonly used intradermal skin tests and the passive transfer test of Prausnitz and Kuester.

### CLINICAL PROCEDURE AND OBSERVATIONS

The purpose of this paper is to report observations on generalized insulin allergy in 8 patients who were studied in the Metabolism Clinic of the Billings Hospital of the University of Chicago during the years 1937 to 1941.

These patients either had developed clinical symptoms of insulin allergy during observation in our clinic or were referred to us because of their symptoms.

In each of these patients the diabetic and allergic histories were taken carefully and all or several of the following tests were performed.

**Insulin skin tests.** Five-hundredths of a cc. of u 40 regular, protamine zinc and commercial crystalline insulin of different brands and origins (beef or pork) were injected intradermally. In 5 patients tests were

TABLE I. CLINICAL FINDINGS AND OBSERVATIONS IN 8 PATIENTS WITH GENERALIZED INSULIN ALLERGY

| Case No.                       | Sex, Age      | Clinical Diagnosis  | Duration of Diabetes, years | Allergic History  | Insulin allergy      |                      |  |   |   | Eosinophilia % |
|--------------------------------|---------------|---|-----------------------------|---|----------------------|----------------------|--|---|---|----------------|
|                                |               |   |                             |   | Onset                |                      |  | Symptoms  |   |                |
|                                |               |   |                             |   | Dur-<br>ing<br>first | After<br>lapse<br>of | Time<br>before<br>first<br>symp-<br>toms | Local   | General   |                |
|                                |               |   |                             |   | Treatment            |                      |  |   |   |                |
| 1, L.H. <sup>1</sup><br>169663 | Female,<br>70 | Diabetes mellitus;<br>cancer of breast;<br>hypertensive heart disease;<br>osteoarthritis  | 8                           | None  | +                    | o                    | 2 wk.                                    | Swelling, redness, itching, induration, erythema                                | Urticaria, esp. in face; pruritus, nausea, vomiting   | 2              |
| 2, R.A. <sup>1</sup><br>193284 | Female,<br>63 | Diabetes mellitus;<br>arterio-sclerosis   | 5                           | Developed allergy against fresh fruit after insulin allergy; son: hay fever |                      | +                    | 9 days                                   | swelling, redness, itching, induration, erythema                                | urticaria, pruritus, swelling of mucus membranes, joint pain, headache, nausea, vomiting, fever | 1-5            |
| 3, W.B. <sup>1</sup><br>253200 | Male,<br>51   | Diabetes mellitus;<br>arterio-sclerosis   | 12                          | None  |                      | +                    | immediately                              | swelling, redness, itching, induration, and erythema                            | urticaria, pruritus, joint pain, fever  | 4              |
| 4, E.S.,<br>259591             | Female,<br>63 | Diabetes mellitus;<br>arterio-sclerosis;<br>obesity   | 1                           | Was allergic against cat-hair when younger                                  | +                    | o                    | 1-2 wk.                                  | swelling, redness, itching, induration, and erythema                            | joint pain  | 2              |
| 5, H.L.,                       | Male,<br>56   | Diabetes mellitus   | 2                           | None  |                      | +                    | 1 wk.                                    | itching, swelling   | urticaria, swelling of mucus membranes, pruritus  | 2              |
| 6, A.L.,<br>252684             | Female,<br>56 | Diabetes mellitus;<br>arterial hypertension   | 6                           | None  |                      | +                    | immediately                              | itching, redness, swelling  | headaches, joint pain, fever  | 2-5            |
| 7, H.L. <sup>1</sup><br>33205  | Male,<br>52   | Diabetes mellitus;<br>diabetic neuritis;<br>arterio-sclerotic heart disease; optic atrophy; old retinitis; complicated cataract | 14                          | None  | +                    |                      | 1 wk.                                    | itching, swelling, redness, erythema  | urticaria, pruritus   | 3              |
| 8, H.CH.,<br>141438            | Male,<br>55   | Diabetes mellitus;<br>general arterio-sclerosis;<br>angina pectoris; pyonephrosis; otitis media                                 | 2                           | None  | +                    |                      | 11 days                                  | itching, swelling, redness, erythema, (persistent for several days), induration | urticaria, headaches  | 5-13           |

<sup>1</sup> The histories of cases 1, 2, 3 and 7 reported in this paper.<sup>2</sup> Himsworth's test for insulin sensitivity was made in cases 2, 3, 4, 6 and 8. In cases 1 and 7 insulin sensitivity or insensitivity was proven by clinical observation.

TABLE 1 CLINICAL FINDINGS AND OBSERVATIONS IN 8 PATIENTS WITH GENERALIZED INSULIN ALLERGY

| Skin Tests   |          |                |        |          | Precipitation Test | Passive Transfer Test | Insulin     |              | Therapy  | Remarks   |
|--------------|----------|----------------|--------|----------|--------------------|-----------------------|-------------|--------------|--|---|
| Cry-stalline | Regu-lar | Pro-tamin zinc | Hu-man | Controls |                    |                       | Sensi-tive? | Insen-sitive |  |   |
| Insulin      |          |                |        |          |                    |                       |             |              |  |   |
| 2+           | 4+       | 3+             | —      | —        | negative           |                       | +           |              | Desensitization with frequent small doses of crystalline insulin, intramuscular injections attempted, both partly successful | Patient died of pneumonia in diabetic ketosis, autopsy  |
| 2+           | 3+       | 3+             | 4+     | 0        | negative           | positive              | +           |              | Desensitization with frequent small doses, 1 m injections attempted, both unsuccessful, control on diet alone                |   |
| 4+           | 4+       | 4+             | 3+     | 0        | 1 10               | positive              | +           |              | Intramuscular injections, control on diet alone  |   |
| 3+           | 2+       | 2+             | 2+     | 0        | negative           |                       |             | +            | Control on diet alone  |   |
| 2+           | 3+       | 3+             | 2+     | 0        |                    | positive              | +           |              | Control on diet alone  |   |
| 2+           | 3+       | 3+             | —      | 0        | 1 5<br>1 10        |                       | +           |              | Intramuscular injections without success, control on diet alone  |   |
| 2+           | 3+       | 3+             | —      | 0        | 1 80               | positive              |             | +            | Intramuscular injections   | Patient developed severe insulin resistance and required during the last 6 months of his life about 1000 u daily no autopsy |
| 2+           | 3+       | 3+             | 3+     | 0        | 1 10<br>1 20       |                       |             | +            | Control on diet alone  |   |



made also with a special insulin prepared from human pancreas.<sup>1</sup> As controls, normal saline and a 0.5 per cent phenol solution were used. The tests were read after 15, 30, 45, 60 minutes and, in some instances, after 3 and 24 hours. Wheal formation, erythema, induration and pseudopods were observed and measured. Only those tests were described as positive in which wheals and pseudopods developed within 60 minutes after injection. Since positive reactions frequently varied in degree with different types of insulin a grading of 1+, 2+, 3+ and 4+ was used for describing the results (table 1). It should be understood that these grades are relative ones and apply only to test differences in the same patient. They cannot be used to compare degrees of allergic response between different patients.

*Passive transfer test (Prausnitz-Kuestner).* One-tenth of a cc. of freshly prepared serum of the patient was injected subcutaneously into the forearm of each of two control persons. A similar injection was made with normal serum. Twenty-four hours later 0.05 cc. of crystalline insulin was injected intradermally into the sensitized areas and a non-sensitized area. Again the occurrence of erythema, wheals, and pseudopods was observed.

*Insulin collodion-precipitation test (Cannon-Marshall).* The tests were performed in Dr. Cannon's laboratory with insulin-coated collodion particles prepared according to the original procedure of the authors (10). The double dilution technique was used, so that the first tube would contain a dilution of serum of 1:5. Then, 0.5 cc. of the insulin-coated particles was added to each tube. Most of the tests were made with unheated sera and with sera heated over a waterbath at 56° C. for 30 minutes. Control tests with crystalline egg albumin-coated particles, normal human sera, uncoated particles and saline were made.

Routine skin tests with the 30 common food and inhalant allergens were performed in the Allergy Clinic (Dr. Harold C. Wagner).

Count of eosinophilic blood cells was made.

The insulin sensitivity test of Humsworth (11) was carried out or other information as to the patient's insulin sensitivity was obtained.

Table 1 gives a comprehensive summary of our findings. The details of four illustrative cases will be found at the end of this paper.

All 8 patients had diabetes and belonged to the middle or higher-age group. Their ages varied between 51 and 70 years, the duration of the diabetes between 1 and 15 years. Three of the patients were males and 5 were females. In 3 instances insulin insensitivity was present, and in one of these (case 7)

the resistance was so severe that for several months more than 1000 u of insulin daily was necessary to check the hyperglycemia.

Only one patient had an allergic history, while in the families of two others, allergic diseases were known. The routine allergy tests were negative in all patients. An increase of eosinophilic cells was found in one patient only, all others having 5 or less than 5 per cent eosinophiles.

Four patients had had previous periods of insulin treatment, during which no or only mild allergic symptoms had been observed. In two of these patients symptoms appeared immediately after resuming the insulin injections. In the 2 others and in the 5 patients in whom insulin allergy had developed during the first course of treatment, first symptoms were noted not earlier than 7 days and not later than 2 weeks after the beginning of the treatment.

The skin tests with the various brands of insulin and especially with crystalline insulin were positive in all patients. The 5 patients who were tested with human insulin showed positive responses to this preparation also. An immediate reaction with erythema, wheals, pseudopods and itching was observed in all patients. These reactions persisted for several hours and usually reached their peak after 60 minutes or later. In 3 instances this reaction was followed by severe generalized symptoms, with urticaria appearing on the arm or the face (lips and eyelids) and general malaise which persisted for more than 24 hours. The controls were negative or showed an occasional slight erythema which disappeared within one hour.

The passive transfer test was performed in 4 patients and was positive in all instances.

The insulin precipitation test was positive in various degrees in 4 of the 7 patients. The highest titers were found in the blood of a patient who was insulin resistant (case 7).

Specific desensitization was successful temporarily in one patient (case 1). In another patient (case 7) treatment with serum from a rabbit which had been sensitized with the patient's blood, as proposed by Karr (12), was attempted and was unsuccessful. Intramuscular administration of insulin partially alleviated the reactions in some cases and was found to be the best of all therapeutic procedures tried, but it did not completely prevent symptoms. In 6 patients it was finally necessary to discontinue insulin.

Although no patient died from allergic reactions, insulin allergy must be considered as a contributory cause in the death of 1 patient (case 1) who died of bronchopneumonia. The symptoms of diabetic acidosis could have been prevented if efficient insulin therapy had been possible. Another patient (case 7) died with severe insulin resistance which had developed after the earlier appearance of insulin allergy.

<sup>1</sup> We are indebted for this preparation to Dr. Paul Cannon, for whom it was made by the Eli Lilly Co., Indianapolis, Ind.

Insulin skin tests were carried out in 44 diabetic patients who were treated with insulin but had no symptoms of generalized insulin allergy. Some of them showed mild and transient local reactions as are frequently observed during the second week of treatment with protamine zinc insulin. None showed a complete series of positive tests. In 8 patients protamine zinc insulin alone, and in 6 regular insulin gave positive reactions. These reactions showed wheals but no pseudopods and did not persist longer than one hour.

#### DISCUSSION

The clinical histories, the positive skin tests with all different brands of commercial insulin, as well as with human insulin and the passive transfer tests seem to prove sufficiently that our patients belong in the group of persons with generalized allergy against the insulin protein itself.<sup>2</sup>

The first question which offers itself is, why are these patients not allergic against their own insulin? None of them was totally diabetic so that the pancreas undoubtedly was still able to produce a certain amount of insulin, yet they were allergic even to injected human insulin. Only speculative answers can be ventured. It may be that the process of extraction alters the insulin molecule, so that even insulin extracted from human pancreas can become an allergen. It may also be that a preexistent allergic disposition is precipitated only if high concentrations of insulin are accumulated subcutaneously. Skin and mucous membranes are the chief organs of allergic response. Under physiologic conditions they are reached by very minute amounts of insulin. This changes if, with the beginning of treatment, insulin depots are placed near the skin. The fact that intramuscular administration of insulin frequently alleviates allergic reactions may point in this direction.

Analysis of our own observations and of those reported in the literature yields certain interesting facts.

**Age distribution.** The 12 cases with generalized allergic reactions and proven insulin allergy referred to by Yasuna (6) and the 3 cases of Herzog (8) and of Hinko and coworkers (9) belonged to the middle-age group as did our patients. Only one patient was younger than 30, the others were between 40 and 71 years of age. It is possible that this reflects simply the age incidence of diabetes, which is low in the first two decades and increases rapidly later. On the other hand, allergic diseases are known to be very frequent in early life. Although the number of observations is

too small to permit statistical conclusions, it is interesting to speculate on the possibility that the tendency toward insulin allergy may be one of the features of diabetes in the middle age group which differs in so many respects from the diabetes of the juveniles.

**Onset of allergic symptoms.** Our observations confirm the finding that lapse of treatment seems to be important for the development of insulin allergy. Nine of the 15 cases in the literature had had previous periods of insulin treatment with intervals from a few months to several years. The long interval between the first and second course of treatment seems to indicate that a sensitization once developed in a pre-disposed individual will not disappear with time, although a few exceptions have been observed (2, 9). It is true that many patients can resume insulin treatment after interruption without untoward effects, but among the total number of persons with generalized insulin allergy, those with lapse in treatment constitute a high percentage. Perhaps, therefore, skin tests or other immunologic studies should be made in every patient who must be placed on insulin therapy for a second time. Also, the possibility of sensitization should be considered in the temporary insulin treatment of non-diabetic patients.

During the first course of treatment the development of insulin allergy seems to be characterized by a latent period. This lasted from 7 to 25 days in the case reports from the literature. This interval indicates the time necessary for the development of sensitization, and it shows also that it is valueless to perform skin tests as a routine procedure in any diabetic patient before beginning insulin therapy for the first time. The allergic predisposition apparently needs a period of sensitization for its activation. Skin tests need be made only when allergic symptoms appear. It may be useful to refer here to two complications of the insulin skin tests which we have observed: a), insulin hypoglycemia and b), delayed reactions. Hypoglycemia can be anticipated and so prevented if many tests with insulin are made simultaneously. Delayed allergic reactions, usually generalized and severe, are likely to occur in patients with severe clinical symptoms. It has been stated that they can be avoided if epinephrin is given after the immediate reaction has been read. The patient should be warned of the possibility of this reaction and sometimes it may be better to perform the passive transfer test first. If this test is positive, skin tests may not be necessary. A negative passive transfer test, however, does not seem to exclude insulin allergy.

**Allergic history.** A history of any allergy should suggest the possibility of allergy to insulin. The majority of diabetic patients with asthma, hay fever and other allergic conditions, however, are able to undergo insulin treatment without any complication.

<sup>2</sup> After this paper was completed, Philip Wasserman and I. Arthur Mursky's paper on "Immunologic identity of insulin from various species" appeared in *Endocrinology* 31: 115, 1942. These authors demonstrated conclusively the immunologic identity of insulin derived from beef, pork, sheep, bison, dog, and man.

although mild local reactions are not uncommon. Skin tests will help to rule out general insulin allergy and to find the least irritating preparation, which will be crystalline insulin in most instances.

Eosinophilia is of little significance in insulin allergy as well as in allergy in general. Patients with insulin allergy do not differ from non-allergic patients in whom no or only a slight eosinophilia has been found in response to insulin injections (4, 13). Moreover, a pre-existent eosinophilia does not indicate danger of insulin allergy.

*Insulin allergy and insulin insensitivity.* In one of our patients insulin allergy preceded the development of severe insulin resistance (case 7). Two other patients were allergic and insensitive at the same time. The insensitivity was established with the Himsworth test (11). Similar observations have been reported in the literature (4) and it has been suggested that both conditions may have the same cause. But, as Harten and Walzer state, 'insulin refractoriness is by no means a constant accompaniment of insulin allergy' (5). The majority of patients with allergic symptoms showed no change in their hypoglycemic response to insulin (5, 6) and, on the other hand, patients with insulin resistance offer allergic symptoms only occasionally (14). In general, both conditions seem to be independent of each other in their symptomatology as well as in the mechanism which causes them.

*Therapy.* Intramuscular administration of insulin, treatment with calcium, histamine, histaminase (15) and epinephrin have been recommended, as well as specific desensitization. The desensitization is performed either by giving multiple graduated doses of insulin at short intervals over a period of several hours, or by giving a very small insulin dose a short time before the therapeutic dose is injected. Good results have been reported in patients with localized allergic reactions. These procedures, however, are not always successful in the presence of generalized insulin allergy. In 6 cases of our series and in 11 of the 15 cases from the literature, the treatment had to be discontinued because of persistence or recurrence of allergic symptoms. Under these circumstances it is a rather fortunate coincidence that the diabetes in most of these patients is of only moderate severity, and with some effort can be controlled by diet alone.

#### SUMMARY

In contradistinction to the rather frequent, mild and transient local allergic reactions after insulin, which mostly are not due to insulin itself but to unspecified substances present in the insulin preparation, generalized insulin allergy is a rare but severe complication in the treatment of diabetes. Observations and immunologic studies on 8 of our cases and 15

from the literature indicate that this condition occurs predominantly in patients of the middle or high-age group with moderately severe diabetes. Interrupted insulin treatment seems to predispose to allergy. Skin tests may be advisable in all patients who resume insulin treatment, and in those who have clinical symptoms suggestive of insulin allergy.

#### CASE REPORTS

*Case 1* gives the history of a patient who developed generalized insulin allergy during the first course of treatment and who was insulin sensitive.

*Case 1, L.H., (169 663),* a female, was 63 years old when diabetes was first diagnosed. For 5 years she followed a diet only, but was never free of polydipsia and polyuria. In 1937, at the age of 68 she came to Billings Hospital because of a lump in the left breast which had developed a few months before hospitalization and because of diabetic symptoms. The tumor was found to be a carcinoma and mastectomy was performed after the diabetes had been brought under control by diet (C 100, P 60, F 150) and 20 u of regular insulin. The postoperative course was uneventful. However, 2 weeks after the insulin treatment had been started the patient began to complain of itching and painful swelling at the site of the injections. These local reactions increased in severity and duration and would reach 'the size of a man's hand.' They became indurated and persisted up to 24 hours. Soon, general symptoms developed. The face became swollen, the eyelids appeared puffy, urticaria was present at various parts of the body and the patient complained of headaches, nausea and vomiting. Skin-tests were made at that time and were positive with various brands of commercial insulin. The patient gave no history of allergic reactions previous to insulin treatment and there was no history of allergy in her family. It was decided to stop the insulin injections and to attempt diabetic control with diet alone. The local reactions disappeared immediately, the general symptoms gradually. The diabetes was controlled on diet for about one year, after which time it became worse. The fasting blood sugar reached 263 mg. per cent and severe glycosuria recurred. A new series of insulin skin tests was positive. Since crystalline insulin gave the mildest reaction, the patient was advised to use 10-0-10 u of this preparation daily. Within a few days the diabetes was under control again, but the previous local and generalized reactions reappeared to an even more severe degree. Therefore intradermal desensitization with minute amounts of crystalline insulin at short intervals was attempted. On the first day a total of 12.4 u was given over a period of 15 consecutive hours at intervals of 30 minutes. The first dose was 0.001 u in 0.1 cc. volume. The doses were increased progressively to a final dose of 1.0 u in 0.25 cc. Only very mild local reactions were noted during this time. On the second day a first dose of 0.1 u was given intradermally, which was followed by subcutaneous injections of 1.0 unit each at hourly intervals. During the following days it became possible to increase the single doses and to decrease the number of injections. Finally, 12 u could be given twice daily and were sufficient for the diabetic control. But,

again, 2 weeks later local and generalized reactions recurred. Gastro-intestinal symptoms with nausea and vomiting and generalized urticaria made it necessary to stop the insulin treatment. The patient tried to manage on diet alone but was not successful. Ten months later, she developed bronchopneumonia and diabetic acidosis. Because of the previous experiences the family physician did not give insulin. When she entered the hospital she was in deep coma, insulin was given immediately, but the patient died a short time after admission. The autopsy (Dr Paul Cannon) revealed lobar pneumonia in the left upper lobe, edema and hypostatic bronchopneumonia in the other lobes. The pancreas showed considerable acinar atrophy and fatty infiltration with marked hyalinization and interstitial fibrosis in the islets of Langerhans. The liver showed fatty infiltration. No significant changes were found in other organs.

Cases 2 and 3 developed generalized insulin allergy after lapse of treatment. Case 2 did not have any allergic symptoms during the first course of treatment, whereas case 3 had already shown local reactions when he received insulin in the first period.

Case 2, R. A., (193 284), a 63 year-old white housewife had been a diabetic patient for about 6 years before she came under our observation in 1938. She was never seriously sick and did not have any symptoms of allergic diseases. However, one of her sons had hay fever. When diabetes was first diagnosed, she was placed on a diet and 20 u of regular insulin. The insulin treatment was discontinued after a few weeks, but it was resumed several times for short periods during the following 3 years. When she was seen in our clinic, the diabetes was under good control on diet alone. However, one year later in the spring of 1940, it seemed advisable to give insulin. The patient was instructed to take 10 u of protamine zinc insulin. Within a week the mild glycosuria, polyuria and general weakness disappeared. On the ninth day of treatment local reactions began to develop which became worse from day to day. At first, swelling, redness and itching were localized at the site of injection and disappeared after several hours. Later the urticaria spread over the body and persisted for more than 24 hours. On the twelfth day she came to the clinic and presented generalized urticaria with the most severe involvement on the inner surfaces of elbows and knees. The lips were swollen and the patient complained of severe headache, joint pain, nausea and vomiting. At that time a passive transfer test was performed which was positive. Insulin was discontinued and the reactions disappeared slowly. Insulin skin tests were performed a week later. They were positive with all tested preparations. The reactions to these tests were severe and persisted for almost 3 days. An attempt at desensitization was unsuccessful because of severe local reactions during this procedure. Intramuscular injections of insulin alleviated the reactions slightly, but the patient insisted on discontinuation of insulin treatment. This was possible after further restriction of the diet. Skin tests in the spring of 1942 gave the same results as the previous tests.

Case 3, W. B., (253 200), was a 51 year old white man with a diabetic history of 12 years' duration. About 10

years ago insulin treatment was begun but soon discontinued because of local reactions which had appeared after the very first injection. When he came to our Clinic in 1939 he complained of general weakness, polydipsia and polyuria, the fasting blood sugar was 179 mg per cent and more than 50 gm of glucose was excreted in the urine during 24 hours. Dietary restriction (C 100, P 75, F 150) was not sufficient to control the diabetes and the patient was advised to take 15 u of protamine zinc insulin. He did so for 10 days and the hyperglycemia as well as the glycosuria improved. But the same reactions recurred which were present 10 years previously. Swelling, redness and itching at the site of injection increased from day to day. After 10 days these reactions became generalized and involved both thighs and legs, shoulders and arms. Knee and elbow joints were swollen and very painful. These reactions persisted for more than 24 hours and were accompanied by headache and slight fever. The patient did not have a history of any other allergic disease, nor were allergic diseases known in his family. The passive transfer test and the insulin skin tests were positive. The skin tests were followed by generalized urticaria and malaise. Similar reactions occurred when insulin was given intramuscularly and when a desensitization was attempted with an intradermal injection of a minute dose of insulin followed by the therapeutic dose subcutaneously. The diabetes was controlled finally by restricted diet alone.

Case 7 represents a condition in which insulin allergy preceded the development of insulin resistance. The complete history of this case will be published separately.

Case 7, H. L., (33 205), a 52-year-old man, came under our observation in December, 1938. As early as 1925 he was told that there was sugar present in the urine. In the following years he developed retinitis, bilateral cataract and arteriosclerotic heart disease. The diabetes did not receive attention, however, until he came to Billings Hospital because of bronchopneumonia and cardiac failure. At that time the fasting blood sugar was normal, but the urine contained sugar. A glucose tolerance test confirmed the diagnosis of diabetes mellitus and the patient was placed on a restricted diet (C 100, P 70, F 150). About 6 months later he began to notice increasing polydipsia and polyuria, neuritic pain in legs and arms, general weakness and weight loss, the fasting blood sugar was found to be 286 mg per cent and the sugar excretion about 10 gm in a 24-hour urine specimen. He was hospitalized and insulin treatment was started. A total of 50 u (30 u of protamine zinc plus 20 u of regular insulin) was necessary to keep the blood sugar within normal limits and the urine sugar free. From the seventh day on, the sites of injection became swollen, red and indurated, itched and were painful for 24 to 48 hours. The appearance of these reactions did not vary with variation of the site of injection (thigh, arm or abdominal wall) or with the type of insulin used (regular, crystalline or protamine zinc insulin). A series of insulin skin tests was performed. All tests were positive. Intramuscular application of insulin was tried and it was found that no or only little local reactions occurred. Therefore this mode of injection was used in the further treat-

ment. The diabetes remained under control on the previous diet and 50 u of insulin daily until 7 months later, when without apparent reason the glycosuria increased. Daily doses of 100 to 200 u of insulin were insufficient for diabetic control and in July, 1940, the patient was hospitalized because of diabetic acidosis. Since massive doses of insulin (1000 u within 24 hours) had very little effect, insulin was given intravenously. After two injections of 100 units each at an interval of one hour general urticaria developed with severe involvement of all sites of previous insulin application. Intramuscular injections were resumed and finally the diabetic acidosis came under control. The passive transfer test with the blood of this patient was positive and the insulin precipitation test was strongly positive. The blood, however, did not inhibit the insulin hypoglycemia in rabbits. Following this acidosis and general allergic reaction, the patient required about 500 to 1000 u of insulin daily, but no satisfactory control of the diabetes could be achieved. An attempt at biological desensitization with the method of Karr and associates (12) was unsuccessful. The patient died 6 months later.

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# Present Status of the Use of Male Sex Hormones and Chorionic Gonadotropins as Growth Stimulating Factors

## [Endocrines and Growth]

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THE VALUE of chorionic gonadotropin as a therapeutic agent in hypogonadism and cryptorchidism, and of the testosterone compounds in eunuchoids and castrates, has been well established. Coincident with the improvement in the genital development of boys under chorionic gonadotropin therapy, an increase in the growth rate beyond the expected average was observed by Lurie and Hertzman (1), Dorff (2), Thompson (3), and by us

Rubinstein and Solomon (4-7) demonstrated an increase in body length of white rats following the administration of moderate doses of testosterone compounds Webster and Hoskins (8) Rapfogel (9), Albright et al. (10), Brown and Ross (11) and Goldzieher (12) used testosterone propionate in children presenting growth deficiency and observed an increase in growth rate in these children and a few adolescents. There are several contradictory reports pertaining to the effect of various hormones on bone growth, bone density and epiphyseal union in rats, mice and guinea pigs. Silberberg (13) showed that after a temporary acceleration, there is a retardation of bone growth. Turner, et al. (14) did not find a difference in the skeletal development between infantile rats treated with testosterone and the controls. McCullagh and McGurl (15) reported an increase in the rate of epiphyseal union in some of their patients treated with testosterone.

### CLINICAL DATA

Of a group of 82 children who received chorionic gonadotropin therapy for various indications such as certain types of cryptorchidism, hypogonadism, adipsogenital dystrophy and growth deficiency, observations were made on growth in 50 cases and the data are reported.

Of another group of 49 children and adolescents receiving various forms of hormonal therapy for primary growth retardation, 15 received testosterone propionate and observations on growth were made. Thus, the total number of cases presented consists of 65 children and adolescents. Each group is analyzed in detail in tables 1 and 2.

Chorionic gonadotropin<sup>1</sup> was administered arbitrarily in the following manner: 100 to 750 i.u. two to three times a week parenterally for periods from 2 months to 2 years, with varying intervals of rest, (table 1).

Testosterone propionate<sup>2</sup> therapy was administered arbitrarily in the following manner: 10 to 25 mg. parenterally twice a week for periods from 3 to 6 months (table 2).

In all cases treated primarily for growth deficiency, and in the majority of cases treated for hypogonadism and cryptorchidism, roentgen-ray studies were made of the skull and long bones at intervals throughout the course of therapy and subsequently. Other laboratory studies included determination of the B M R, Wassermann reaction, blood sugar, cholesterol, calcium, phosphorus and phosphatase, complete blood studies and routine urinalysis.

The data for each patient were tabulated in the group in which they fell at the time of the first visit. At the last visit, before the final computation of the data in this paper, the height was measured and tabulated. Any change in grouping was estimated and recorded, an estimate of the average of increase, the *status quo* and the decrease in growth rate was made in each case.

<sup>1</sup> Chorionic gonadotropin (A.P.L.) and anterior pituitary extract (Growth Complex) were supplied through the courtesy of Ayerst, McKenna and Harrison, Montreal, Quebec and Rouses Point, N. Y.

<sup>2</sup> Testosterone propionate (Oreton) was supplied through the courtesy of Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J.

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TABLE I EFFECT OF CHORIONIC GONADOTROPIN ON GROWTH

| Case   | Age    | Chief Complaint          | Duration of Therapy | Total Amount | Initial Ht. and Date | Ht. and Date at End of Therapy | Growth Increase | Latest Ht. and Date   | Growth after Cessation of Therapy | Progress in Burgess Grouping <sup>1</sup> |
|--------|--------|--------------------------|---------------------|--------------|----------------------|--------------------------------|-----------------|-----------------------|-----------------------------------|---|
| 1, DF  | yr. 14 | Growth retardation       | mo. 13              | I.U. 26,000  | in. 9/27/34<br>46.75 | in. 10/12/35<br>51.25          | in. 4.50        | in. 10/30/37<br>57.00 | in. 5.75                          | % +1                                      |
| 2, SM  | 6.5    | Cryptorchidism           | 10                  | 34,500       | 8/ 3/35<br>47.00     | 11/21/36<br>48.50              | 1.50            | 9/21/40<br>56.75      | 8.2                               | 0   |
| 3, JS  | 8      | Cryptorchidism           | 3                   | 8,000        | 2/19/35<br>47.50     | 8/12/35<br>49.75               | 2.25            | *                     |                                   | +30                                       |
| 4, IK  | 5.5    | Cryptorchidism           | 3.5                 | 4,200        | 3/ 1/36<br>44.25     | 3/ 1/37<br>46.75               | 2.50            | 3/25/42<br>59.00      | 12.25                             | +30                                       |
| 5, EM  | 6      | Cryptorchidism           | 4                   | 17,000       | 6/ 8/36<br>49.75     | 2/18/38<br>53.50               | 3.75            | 6/17/42<br>61.75      | 8.25                              | 0   |
| 6, RO  | 15     | Adiposogenital dystrophy | 3                   | 18,000       | 9/12/36<br>61.00     | 3/27/37<br>63.00               | 2.00            | 2/19/38<br>65.25      | 2.25                              | +2  |
| 7, IS  | 4      | Cryptorchidism           | 24                  | 131,200      | 2/11/36<br>44.00     | 2/18/39<br>51.50               | 7.50            | 5/ 2/42<br>56.00      | 4.50                              | +10                                       |
| 8, HS  | 12     | Cryptorchidism           | 3                   | 45,000       | 11/24/36<br>55.75    | 3/ 4/37<br>56.50               | 0.75            | 11/26/38<br>59.00     | 2.50                              | -10                                       |
| 9, AS  | 6      | Cryptorchidism           | 2                   | 10,000       | 9/22/36<br>45.00     | 11/21/36<br>48.50              | 3.50            | *                     |                                   | +43                                       |
| 10, JC | 10     | Cryptorchidism           | 16                  | 53,500       | 6/ 8/37<br>53.00     | 10/29/38<br>55.75              | 2.75            | 12/ 3/38<br>56.75     | 1.00                              | +20                                       |
| 11, LD | 8      | Cryptorchidism           | 5                   | 25,000       | 10/16/37<br>49.00    | 9/24/38<br>49.00               | 0.00            | 6/13/42<br>60.25      | 11.25                             | -20                                       |
| 12, RL | 3.5    | Cryptorchidism dystrophy | 23                  | 93,500       | 10/30/37<br>35.00    | 1/11/41<br>50.00               | 15.00           | 5/16/42<br>54.50      | 4.50                              | +79                                       |
| 13, HS | 11     | Hypogonitalism           | 4                   | 24,000       | 5/ 1/37<br>54.50     | 3/28/39<br>56.50               | 2.00            | 2/ 6/40<br>58.50      | 2.00                              | -25                                       |
| 14, EW | 7      | Hypogonitalism           | 6                   | 36,000       | 9/11/37<br>47.75     | 3/25/40<br>53.00               | 5.25            | 2/28/42<br>57.00      | 4.00                              | +20                                       |
| 15, MF | 11     | Cryptorchidism           | 3                   | 15,000       | 12/24/38<br>53.50    | 3/24/39<br>53.50               | 0.00            | 6/ 6/42<br>61.00      | 7.50                              | 0   |
| 16, SG | 1      | Cryptorchidism           | 4                   | 20,000       | 12/ 2/38<br>32.75    | 4/ 4/39<br>35.00               | 2.25            | 6/27/41<br>40.50      | 5.50                              | +48                                       |
| 17, EM | 11     | Cryptorchidism           | 3.5                 | 17,000       | 10/29/38<br>53.00    | 2/ 4/39<br>53.50               | 0.50            | 9/28/40<br>57.25      | 3.75                              | +10                                       |
| 18, HN | 7      | Cryptorchidism           | 2                   | 9,000        | 10/29/38<br>50.00    | 2/18/39<br>51.00               | 1.00            | 9/21/40<br>55.00      | 4.00                              | +7  |
| 19, HN | 10     | Growth retardation       | 14                  | 84,000       | 8/23/38<br>49.00     | 6/ 1/40<br>52.75               | 3.75            | 2/14/42<br>59.00      | 6.25                              | +26                                       |
| 20, JW | 18     | Hypogonitalism           | 2                   | 8,000        | 3/29/38<br>61.00     | 11/ 1/38<br>63.75              | 2.75            | 4/ 7/42<br>66.25      | 2.50                              | +30                                       |
| 21, LA | 8      | Cryptorchidism           | 2                   | 17,000       | 3/ 7/39<br>43.50     | 6/22/39<br>49.00               | 5.50            | 10/19/40<br>51.50     | 2.50                              | +50                                       |
| 22, MA | 7.5    | Adiposogenital dystrophy | 5                   | 22,000       | 6/11/39<br>54.00     | 11/27/39<br>56.25              | 2.25            | 4/23/38<br>57.50      | 1.25                              | 0   |
| 23, HD | 7      | Cryptorchidism           | 2                   | 6,000        | 5/ 6/39<br>45.25     | 7/10/39<br>45.75               | 0.50            | 11/23/40<br>48.50     | 2.75                              | 0   |

TABLE 1 (Cont'd)

| Case   | Age   | Chief Complaint          | Duration of Therapy | Total Amount   | Initial Ht and Date      | Ht. and Date at End of Therapy | Growth Increase | Latest Ht. and Date     | Growth after Cessation of Therapy | Progress in Burgess Grouping <sup>1</sup> |
|--------|-------|--------------------------|---------------------|----------------|--------------------------|--------------------------------|-----------------|-------------------------|-----------------------------------|---|
| 24, JC | 37-10 | Hypogonitalism           | mo 4                | 1 U.<br>22,000 | in.<br>11/ 4/39<br>54 50 | in.<br>9/21/40<br>56 25        | in<br>1.75      | in.<br>2/14/42<br>58 75 | in<br>2.50                        | %<br>0                                    |
| 25, RF | 5     | Cryptorchidism           | 11                  | 40,000         | 10/28/39<br>43.50        | 9/21/40<br>45.00               | 1 50            | *                       |                                   | +20                                       |
| 26, WH | 10    | Cryptorchidism           | 8                   | 32,000         | 8/31/39<br>52.25         | 10/19/40<br>54.50              | 2 25            | *                       |                                   | 0   |
| 27, RS | 12    | Cryptorchidism           | 3                   | 24,000         | 9/12/39<br>52.75         | 6/20/40<br>54.25               | 1.50            | 6/13/42<br>59 25        | 5.00                              | +4  |
| 28, DS | 12    | Cryptorchidism           | 5                   | 30,000         | 12/29/39<br>60 50        | 3/ 1/41<br>63.75               | 3 25            | 6/ 6/42<br>68.75        | 5.00                              | +4  |
| 29, NZ | 4     | Hypogonitalism           | 6                   | 14,400         | 1/ 3/39<br>42.25         | 7/11/39<br>44.75               | 2.50            | *                       |                                   | +13                                       |
| 30, DC | 8     | Adiposogenital dystrophy | 10                  | 40,000         | 1/ 3/39<br>55.75         | 1/ 3/40<br>57.25               | 1.50            | 6/ 1/42<br>60 50        | 3 25                              | 0   |
| 31, RB | 7     | Cryptorchidism           | 10                  | 29,500         | 11/16/40<br>47.50        | 11/ 8/41<br>51.50              | 4.00            | 5/ 9/42<br>52.25        | 0 75                              | +40                                       |
| 32, MB | 16 5  | Growth retardation       | 3                   | 8,000          | 10/19/40<br>55.50        | 3/22/41<br>56 25               | 0 75            | 5/ 9/42<br>60 25        | 4 00                              | +5  |
| 33, SG | 5     | Cryptorchidism           | 4.5                 | 27,000         | 9/ 9/40<br>43.50         | 2/ 8/41<br>44.00               | 0 50            | 12/20/41<br>47 00       | 3 00                              | +15                                       |
| 34, SH | 18    | Growth retardation       | 3                   | 9,000          | 9/ 7/40<br>56 75         | 12/14/40<br>57.00              | 0.25            | 7/ 1/41<br>57.00        | 0                                 | 0   |
| 35, DL | 5 5   | Hypogonitalism           | 6                   | 10,450         | 10/17/40<br>48 50        | 4/27/41<br>50.00               | 1.50            | *                       |                                   | 0   |
| 36, BR | 11    | Cryptorchidism           | 2                   | 15,000         | 1/11/40<br>57 00         | 8/ 5/41<br>60 25               | 3.25            | 12/30/41<br>61.00       | 0.75                              | 0   |
| 37, JS | 5     | Cryptorchidism           | 5                   | 14,250         | 3/21/40<br>43 00         | 3/ 1/41<br>46.00               | 3.00            | 4/25/42<br>49 25        | 3 25                              | +10                                       |
| 38, RD | 15 5  | Growth retardation       | 4                   | 16,000         | 5/29/41<br>59 00         | 10/ 4/41<br>60.75              | 1 75            | 5/23/42<br>61.00        | 0.25                              | 0   |
| 39, WD | 7     | Cryptorchidism           | 3                   | 18,000         | 11/15/41<br>58 00        | 3/21/42<br>59 75               | 1 75            | 5/23/42<br>60.25        | 0 50                              | +2  |
| 40, RJ | 11    | Cryptorchidism           | 5                   | 22,000         | 12/20/41<br>53.25        | 5/16/42<br>55.25               | 2 00            | 6/16/42<br>55.50        | 0 25                              | +15                                       |
| 41, MN | 7     | Growth retardation       | 5                   | 9,000          | 11/15/41<br>45 00        | 4/25/42<br>46 25               | 1 25            | 6/ 9/42<br>46.75        | 0 50                              | 0   |
| 42, SS | 16    | Hypogonitalism           | 6                   | 24,000         | 3/ 1/41<br>62.75         | 9/16/41<br>63.75               | 1 00            | 5/16/42<br>64 75        | 1 00                              | +11                                       |
| 43, WS | 11    | Hypogonitalism           | 3                   | 16,000         | 4/19/41<br>57 00         | 7/12/41<br>57 50               | 0 50            | 8/14/41<br>58 50        | 1 00                              | +6  |
| 44, WS | 7.5   | Cryptorchidism           | 4                   | 4,000          | 3/15/41<br>50 75         | 7/16/41<br>52.00               | 1 25            | 4/ 9/42<br>53 25        | 1 25                              | +3  |
| 45, WS | 9     | Hypogonitalism           | 3 5                 | 13,000         | 7/17/41<br>53 50         | 11/29/41<br>54 25              | 0.75            | *                       |                                   | 0   |
| 46, AT | 9     | Adiposogenital dystrophy | 5                   | 25,000         | 12/13/41<br>58 75        | 5/11/42<br>60 00               | 1 25            | *                       |                                   | -3  |



TABLE 1 (Cont'd.)

| Case   | Age       | Chief Complaint    | Duration of Therapy | Total Amount   | Initial Ht. and Date    | Ht. and Date at End of Therapy | Growth Increase | Latest Ht. and Date | Growth after Cessation of Therapy | Progress in Burgess Grouping <sup>1</sup> |
|--------|-----------|--------------------|---------------------|----------------|-------------------------|--------------------------------|-----------------|---------------------|-----------------------------------|---|
| 47, JC | yr.<br>11 | Growth retardation | mo.<br>2            | I.U.<br>12,000 | in.<br>3/ 7/42<br>48.75 | in.<br>5/23/42<br>49.25        | in.<br>0.50     | in.<br>**           | in.                               | %<br>+5                                   |
| 48, MC | 14        | Growth retardation | 2                   | 12,000         | 3/ 7/42<br>53.75        | 5/23/42<br>54.25               | 0.50            | **                  |                                   | +2  |
| 49, LG | 11        | Cryptorchidism     | 4                   | 20,000         | 1/17/42<br>55.00        | 5/16/42<br>56.00               | 1.00            | 6/16/42<br>56.25    | 0.25                              | 0   |
| 50, RH | 9.5       | Cryptorchidism     | 3                   | 21,500         | 1/20/42<br>56.50        | 4/10/42<br>58.00               | 1.50            | *                   |                                   | +4  |

<sup>1</sup> The difference between the initial and final grouping constitutes the percentage of improvement or retardation for each individual child.  
\* Did not report for final check-up.  
\*\* Therapy discontinued recently.

CLINICAL OBSERVATIONS

The administration of chorionic gonadotropin and testosterone propionate was followed in most instances by an acceleration of the growth rate as com-

and social attitude. In the instances in which development of external genitalia preceded the improvement in height therapy was discontinued either temporarily or permanently.

In the group of children who showed improvement under chorionic gonadotropin therapy the percentage of improvement ranged between 1 and 79 per cent as estimated from the Burgess charts, the average improvement being 18.2 per cent. In the group of children treated with testosterone propionate the percentage of improvement ranged from 2 to 30 per cent, the average being 10.9 per cent. Two cases receiving chorionic gonadotropin and one receiving testosterone propionate are reported.

CASE REPORTS

Case 12 (table 1), R.F.L., was first seen in the Endocrine Clinic Oct. 30, 1937, at the age of 3.5 years because of genital and mental retardation and a speech defect consisting of stuttering and indistinct enunciation. At the time of admission the height was 35 inches and the weight 38 lb. (fig. 1, a). There was a retardation in the genital development; the penis was very small, scrotum was contracted and empty, small pea-size testes were located at the external ring. Roentgenograms of the long bones did not reveal any abnormalities of bone development. The sella turcica was somewhat small for the age.

The child was placed on chorionic gonadotropin therapy 500 i.u. two to three times per week. On June 28, 1938, the height was 41.5 inches, an increase of 6 inches in a period of 8 months. The general status had improved; he became alert, his speech was cleared, and he displayed an interest in people and his surroundings. The genitalia (fig. 1, b) showed a marked increase in size; both testes were normal size, the left was in the lower, and the right in the upper part of the scrotum. Treatment was continued with intervals of rest, and roentgen-ray examination of the wrists and hands in 1939 showed an advance in

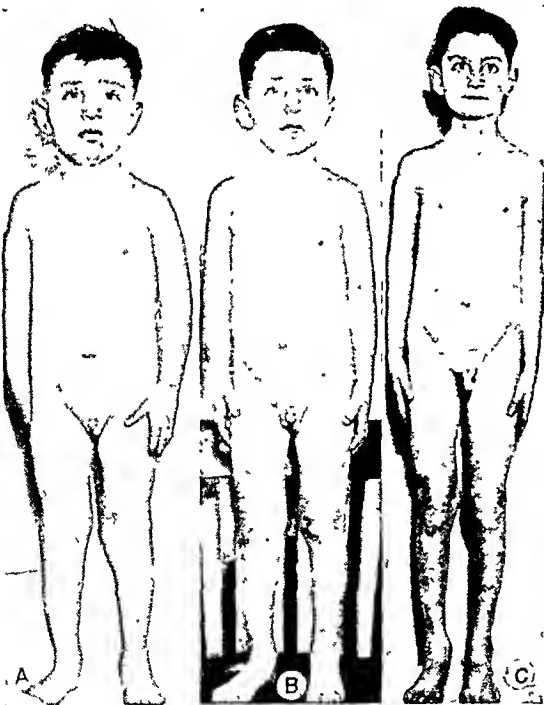


FIG. 1. A. Case 12 (table 1). R. F. L., age 3.5 years; height, 35 in.; Oct. 30, 1937. B. Patient, age 4 years and 2 mo.; height, 41.5 in.; June 28, 1938. C. Patient, age 7 years and 8 mo.; height 4 ft., 1 in.; Dec. 6, 1941. Chorionic gonadotropin therapy. See case reports.

red with the Burgess chart standards. In addition the improvement in stature, other effects observed were development of secondary sex characteristics and improvement in general vitality, mental alertness

TABLE 2 EFFECT OF TESTOSTERONE PROPIONATE ON GROWTH

| Case  | Age   | Chief Complaint                       | Duration of Therapy | Total Amount | Initial Ht and Date | Ht and Date at End of Therapy | Growth Increase | Latest Ht and Date | Growth after Cessation of Therapy | Progress in Burgess Grouping <sup>1</sup> |
|-------|-------|---------------------------------------|---------------------|--------------|---------------------|-------------------------------|-----------------|--------------------|-----------------------------------|---|
| 1 EB  | yr 13 | Growth retardation                    | mo 6                | mg 1,200     | in 8/10/41<br>55 00 | in. 2/18/42<br>58 00          | in 3 00         | in *               | in                                | % +8                                      |
| 2 MB  | 17    | Growth retardation                    | 6                   | 1,200        | 7/ 8/41<br>57 50    | 1/21/42<br>60 00              | 2 50            | 5/ 9/42<br>60 25   | 0 25                              | +5  |
| 3 JC  | 10 5  | Growth retardation                    | 4                   | 800          | 9/16/41<br>47 25    | 1/10/42<br>47 75              | 0 50            | 5/23/42<br>49 25   | 1 50                              | +5  |
| 4 MC  | 13    | Growth retardation                    | 2                   | 300          | 12/ 7/41<br>53 25   | 2/10/42<br>53 50              | 0 25            | 5/23/42<br>54 25   | 0 75                              | +2  |
| 5 JC  | 12    | Cryptorchidism                        | 2                   | 110          | 12/ 3/38<br>56 75   | 4/29/38<br>57 00              | 0 25            | 12/ 6/41<br>64 50  | 7 50                              | +20                                       |
| 6 HC  | 8     | Growth retardation                    | 4                   | 300          | 9/ 1/42<br>47 25    | 1/31/42<br>49 25              | 2 00            | 3/20/42<br>50 25   | 1 00                              | +25                                       |
| 7 CW  | 11    | Growth retardation                    | 3                   | 300          | 7/22/41<br>55 00    | 11/22/41<br>56 50             | 1 50            | 2/28/42<br>57 00   | 0 50                              | +20                                       |
| 8 AF  | 14    | Growth retardation                    | 2 5                 | 500          | 6/14/41<br>57 50    | 10/18/41<br>58 00             | 0 50            | 5/ 9/42<br>60 50   | 2 50                              | +5  |
| 9 LA  | 10    | Growth retardation                    | 4                   | 120          | 7/10/41<br>45 50    | 11/15/41<br>47 00             | 1 50            | 6/ 6/42<br>48 25   | 1 25                              | +3  |
| 10 RR | 14    | Growth retardation                    | 3                   | 575          | 5/10/41<br>57 25    | 11/29/41<br>59 00             | 1 75            | 6/ 6/42<br>60 50   | 1 50                              | +5  |
| 11 SS | 16 5  | Growth retardation and hypogenitalism | 4                   | 800          | 9/16/41<br>63 75    | 1/10/42<br>64 50              | 0 75            | 5/16/42<br>64 75   | 0 25                              | +11                                       |
| 12 WS | 15    | Growth retardation                    | 4                   | 690          | 6/14/41<br>57 50    | 2/28/42<br>60 00              | 2 50            | 5/ 9/42<br>60 75   | 0 75                              | +11                                       |
| 13 NW | 11 5  | Hypogenitalism                        | 2                   | 160          | 3/17/40<br>63 00    | 5/27/40<br>63 75              | 0 75            | 6/20/42<br>66 75   | 3 00                              | -3  |
| 14 RD | 16    | Growth retardation                    | 6                   | 200          | 10/ 4/41<br>60 75   | 5/ 8/42<br>61 00              | 0 25            | **                 |                                   | 0   |
| 15 JW | 18    | Hypogenitalism and growth retardation | 36                  | 1,440        | 11/ 1/38<br>63 75   | 1/ 6/41<br>65 75              | 2 00            | 4/ 7/42<br>66 25   | 0 50                              | +11                                       |

<sup>1</sup> See footnote to table 1

\* Did not return for final check up

\*\* Therapy recently discontinued

development beyond his chronological age. Hormonal therapy was, therefore, discontinued and instructions were given concerning nutritional and vitamin requirements. When seen again on May 7, 1940, he was 48 5 inches in height and weighed 48 25 lb. Since some regression in the genitalia had occurred, therapy was resumed and continued for a period of 4 months after which time it was again discontinued because of a favorable and sufficient response. On Dec 6 1941, he was 53 5 inches tall and weighed 60 lb. The genital development (fig 1, c) was normal but roentgenograms of the wrists and hands still showed the bone age to be in advance of the chronological age. The growth rate continued to be accelerated, however, as noted in the accompanying growth chart (fig 2)

Case 18 (table 1), H N, was admitted to the Endocrine Clinic on July 19, 1937, at the age of 9 5 years. The boy was brought to the clinic by a guardian from the corrective institution to which he had been committed for repeated offenses, such as theft and arson. He and a group of boys of whom he seemed to be the leader, had started about 12 neighborhood fires. It occurred to the Judge, noting the child's stunted growth that these criminal tendencies may have resulted from the child's resentment of his stature, and if this could be corrected, the child might overcome his anti social attitude.

At the time of admission the height was 46 75 inches and weight 50 5 lb. Physical examination revealed short stature and normal genitalia, the facial expression was

stubborn and resentful (fig. 3,a). Roentgen-ray examination of the sella turcica and long bones did not show any abnormality in bone development.

Therapy with anterior pituitary growth extracts<sup>1</sup> was initiated on Aug. 19, 1937, 1 to 2 cc. being administered parenterally 2 to 3 times per week. This therapy was continued with intervals of rest of one month every 2 to 3

therapy. The boy's physical and genital development showed normal progress (fig. 3, c).

When last seen, Feb. 12, 1942, the height was 59 inches, an increase of 5 inches over a period of 16 months following cessation of therapy and a total increase of 12.25 inches over a period of 4 years and 7 months. Roentgen-ray examination of the hands and wrists when the boy was last seen at the age of 14, revealed the osseous and epiphyseal development to be normal for his age. As far as the behavior problem is concerned, the boy continued to improve steadily, and has been paroled in the custody of his parents for the last 2 years.

Case 2 (table 2), M.B., was first seen on Aug. 2, 1940, in the Endocrine Clinic for stunted growth at the age of 16. The height was 54.75 inches and the weight was 76.75 lb. Physical examination (fig. 4, a) showed the boy to be of short stature with a childish facial expression, no pubic hair, and with small penis, scrotum and testes, although the latter were in normal position. Roentgen-ray examination of the hands and wrists on Aug. 15, 1940, revealed a retardation of bone growth and delay in epiphyseal union.

Therapy with anterior pituitary growth extract was initiated on Aug. 15, 1940, and on Nov. 23, 1940, chorionic gonadotropin was added, because there was no demonstrable increase in growth rate. The hormones were administered simultaneously, but in separate syringes. This therapy was continued with brief periods of rest until

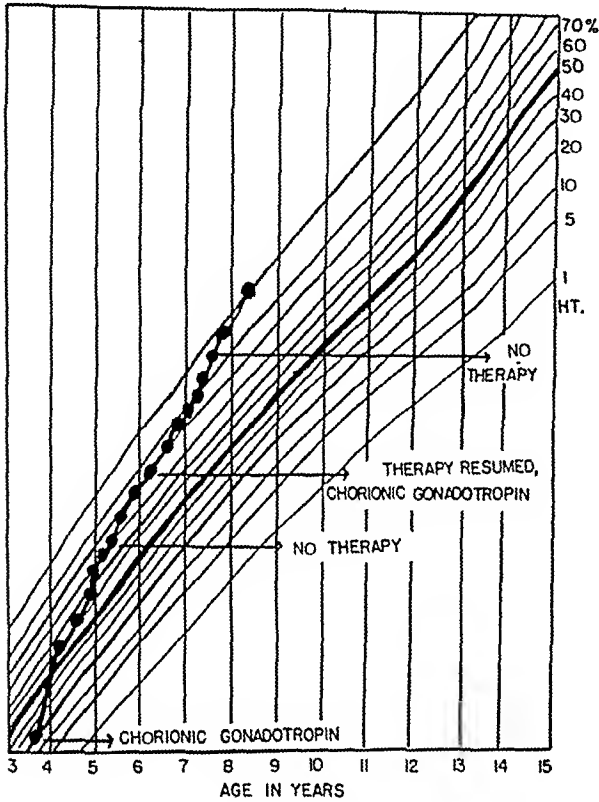


FIG. 2. Growth chart of case 12 (table 1), from 3.5 to 8.5 years of age.

months until November, 1938, at which time the height was 49 inches and the weight 57 lb. Although this was an increase of 2.25 inches in 15 months, there was no increase in the growth rate. Since the boy's growth was of primary interest, therapy was changed to chorionic gonadotropin, because satisfactory results had been obtained in other cases. This therapy, with irregular periods of rest was maintained until May 19, 1939, at which time the height was 49.75 inches and the weight 57.5 lb.

There was a marked development of the genitalia (fig. 3, b). The boy's behavior improved so that he was paroled in the custody of foster parents, the atmosphere of his own home being considered unsuitable at that time.

After an interruption of 3 months in treatment, therapy was resumed and continued until Oct. 25, 1940, at which time the height was 54 inches and weight 73.5 lb. Thus, in 3 years he grew 7.25 inches.

Roentgen-ray examinations of the hands and wrists on May 9, 1939, and Oct. 25, 1940, did not reveal any significant changes. The bony development was in harmony with the advancing chronological age. Therapy was then discontinued and the child was not seen again until May 15, 1941, at which time the height was 56.5 inches, an increase of 2.5 inches in 7 months following cessation of

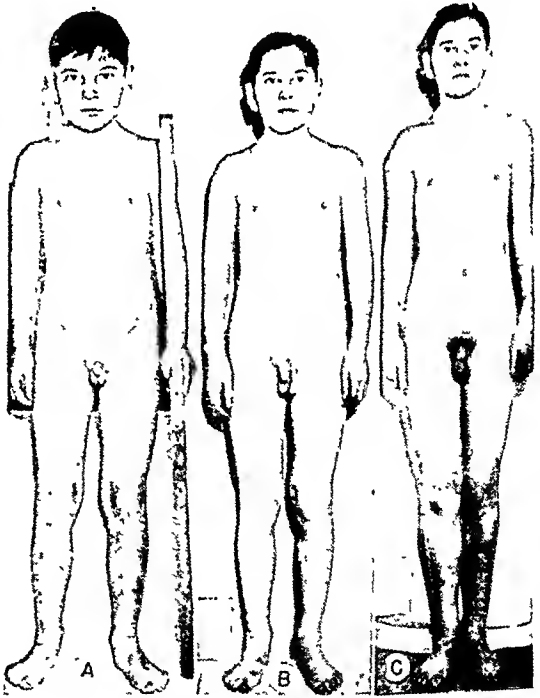


FIG. 3. A. Case 18 (table 1). H. N., age 9.5 years; height 46.75 in.; July 19, 1937. B. Patient, age 11 years, 4 mo.; height 49.75 in.; May 9, 1939. C. Patient, age 13 years and 4 mo.; height, 4 ft., 8.5 in.; May 15, 1941. Chorionic gonadotropin therapy. See case reports.

July 8, 1941, at which time the height was 57.5 inches and the weight was 93 lb. Physical examination revealed marked maturation of the facial expression, an increased development of the chest and arms, and development of

external genitalia (fig. 4, b) Roentgenograms made on July 9, 1941, revealed no change from the findings of the previous examination. On July 10, therapy with testosterone propionate was initiated, 25 mg being administered twice a week. This form of therapy was given for the purpose of increasing the rate of growth, and was continued until Nov. 15, 1941, at which time the height was 59 inches and the weight was 105 1/2 lb. While receiving therapy with growth hormones and chorionic gonadotropin this patient grew 3 inches in 13 months, a growth of 1 1/2 inches in 4 months was noted during testosterone propionate therapy. Roentgen-ray examination on Dec. 6, 1941, still showed a delay in bony development. Therapy with testosterone propionate was resumed on Jan. 31, 1942, at which time the height was 59 1/2 inches and the weight was 105 1/2 lb. Testosterone therapy was discontinued one month later and on May 16, 1942, the height was 60 1/2 inches, the weight 107 lb. Physical examination revealed further progress in muscular development, maturation of the facial expression and development of the genitalia and pubic hair (fig. 4, c). Roentgenograms of the hands and wrists on March 7, 1942, showed the same relative retardation in bone development as was seen before therapy was initiated.

#### DISCUSSION

Administration of chorionic gonadotropin for hypogonadism, cryptorchidism and adipsogenital dystrophy is a generally accepted form of therapy, and has been employed by us for the last 8 years. While treating hypogonadism and cryptorchidism with chorionic gonadotropin we were impressed by the growth stimulating potentialities of this form of therapy. Observations were made on 50 children who received chorionic gonadotropin and it was noted that the best growth response occurred in those patients who presented mainly symptoms of hypogonadism and cryptorchidism. In those patients who presented symptoms of growth retardation chiefly, the chorionic gonadotropin was moderately effective. Of this group 62 per cent (31 children) showed an increase in the rate of growth, 30 per cent (15 children) maintained the original rate of growth and 8 per cent (4 children) were below the original rate of growth. No abnormal findings were noted except in 2 patients in whom there occurred a stimulation of bone growth and development beyond the chronological age.

The use of testosterone as a growth stimulating factor in children is a recent approach to the problem of growth and has been used by us for one year, although its value in the treatment of eunuchs and eunuchoids has been known for some time. Kochakian (16) and Kenyon et al. (17, 18) have demonstrated that the administration of testosterone compounds to experimental animals causes nitrogen retention which is essential for muscular and skeletal growth. Because of the suggested possibility of early bone

maturation, roentgenograms were made from time to time during and subsequent to periods of therapy and because of the effect of the testosterone compounds on the development of external genitalia in boys, the genitalia were frequently examined.

Fifteen children with growth retardation were

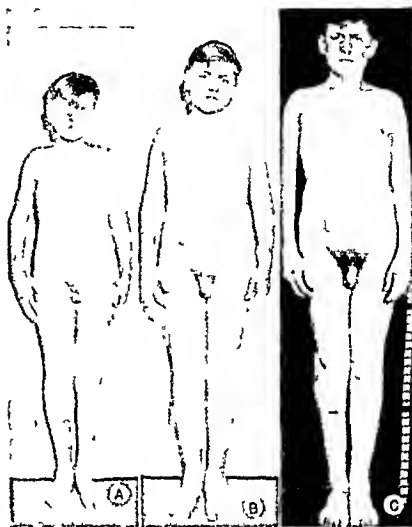


FIG. 4. A Case 2 (table 2) M. B., age 16 years, height 4 ft. 6 7/8 in., Aug. 2, 1940. B Patient, age 17 years, height 4 ft. 9 5/8 in., July 10, 1941. C Patient, age 18 yr., height 5 ft., May 16, 1942. Testosterone propionate therapy. See case reports.

maintained under this form of therapy, and to date no harmful effects have been observed in these patients. When the genitalia showed a tendency to over-development therapy was discontinued. Of this group of 15 children, 13 showed an increase in the rate of growth, one maintained the original rate of growth and in one child the original rate of growth was lowered. Roentgen studies of the long bones were made at frequent intervals and at no time was there an indication of premature epiphyseal union. One year after the initiation of this therapy, the epiphyses remained open as noted at the time when treatment was begun, there was no marked change in bone density.

#### SUMMARY

Growth observations were made on 50 children treated with chorionic gonadotropin and on 15 children treated with testosterone compounds.

Chorionic gonadotropin was administered in doses of 100 to 750 IU two to three times a week for

stubborn and resentful (fig. 3, a). Roentgen-ray examination of the sella turcica and long bones did not show any abnormality in bone development.

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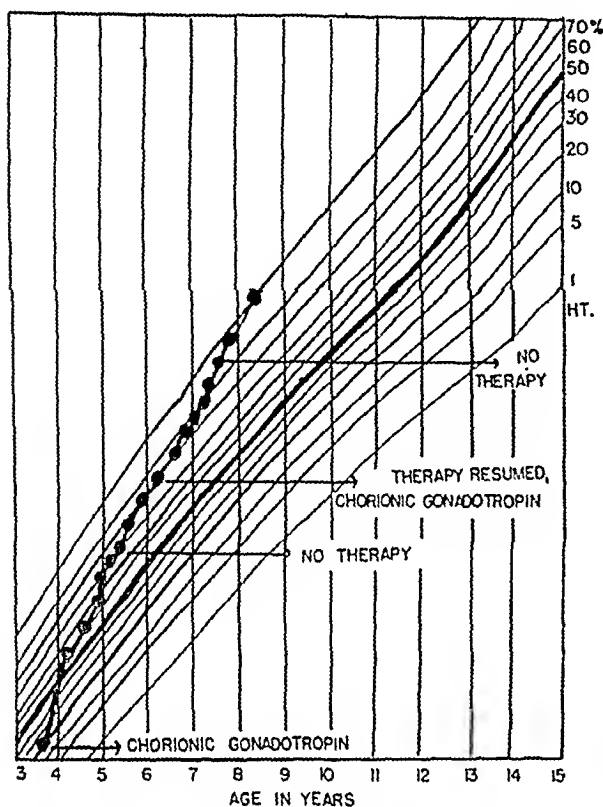


FIG. 2. Growth chart of case 12 (table 1), from 3.5 to 8.5 years of age.

months until November, 1938, at which time the height was 49 inches and the weight 57 lb. Although this was an increase of 2.25 inches in 15 months, there was no increase in the growth rate. Since the boy's growth was of primary interest, therapy was changed to chorionic gonadotropin, because satisfactory results had been obtained in other cases. This therapy, with irregular periods of rest was maintained until May 19, 1939, at which time the height was 49.75 inches and the weight 57.5 lb.

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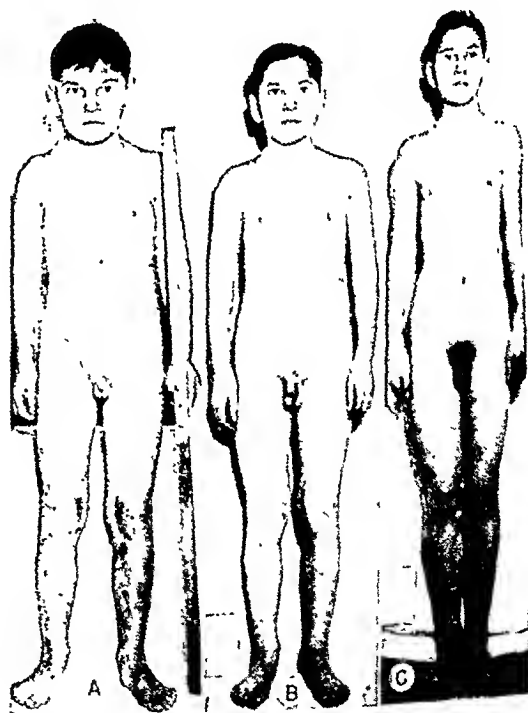


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## THE PARATHYROIDS AND PSYCHOSIS

IN VIEW of the intimate relationship between the parathyroid glands and calcium metabolism and of the influence of calcium upon the functions of the cells of the nervous system, it might be assumed that these glands would play an important rôle in clinical neurological and mental disturbances. In particular, hypoparathyroidism with its accompanying depression in the level of blood calcium might be expected to give rise, to, or to exaggerate, clinical disorders in which hyper irritability is a notable feature. Whether, or to what extent, such is the case is not adequately known except as to the condition, tetany parathyroprævia.

In the older literature Timme described a syndrome in which the patients showed marked irascibility, flying into ungovernable rage upon slight provocation and reacting with irrational violence. Under treatment with parathyroid extract, calcium and sunlight a marked improvement in the disposition was seen. Subsequently Shannon reported the cases of 8 children who developed convulsions followed by depression and irrational speech. As the condition progressed, night terrors, acute manic excitement with screaming, fighting and tearing of the clothes occurred. In 6 of the cases the condition was relieved by parathyroid extract.

Text books of psychiatry and of medicine lay little stress upon the relationship of parathyroid disorders to mental conditions, although for nearly a century it has been recognized that psychosis may develop during the course of clinical tetany. In a recent article Greene and Swanson\* have reported that they had been able to find in the literature of the preceding 19 years only 4 cases in which psychosis appeared as a complication of tetany. Having themselves, however, noted 5 such cases in 18 patients with hypoparathyroidism observed in their own clinic, they surmised that the association is actually more frequent than is commonly recognized.

In their cases, as well as those reported in the earlier literature, the usual type of psychosis was a toxic delirium although other types, including dementia, have been noted. There is, however, apparently no specific type of psychosis which is actually characteristic of parathyroid deficiency. Among the nervous symptoms often seen in this condition are anxiety, depression, and a sense of impending disaster. When the condition reaches the severity of an actual psychosis, delusions and hallucinations appear. In 2 of the cases reported by Greene and Swanson the hallucinations were of a sexual type and in both instances the eroticism had been markedly augmented prior to the onset of the psychosis. Delusions of persecution occurred in 2 other cases and suicide was attempted in both instances.

\* Psychosis in hypoparathyroidism, with a report of five cases. GREENE J. A. and L. W. SWANSON. *Ann. Int. Med.* 14: 1233, 1941.

According to the scanty evidence now available, it appears that if a psychosis does occur in the course of parathyroid tetany it develops within the first 3 or 4 months of that disorder although it may appear within a few days or may be delayed several weeks. The authors comment that psychic disturbances may be the first and only manifestation observed and that the etiology of the psychosis may be missed unless search is made for the characteristic signs of parathyroid deficiency. Frank carpopedal spasms and convulsions are usually absent from the picture.

The prognosis in this psychosis is usually good although the condition may persist for several months. Upon the institution of treatment for the glandular condition there is usually a delay in the mental improvement of from 1 to 4 weeks after the calcium level has been normalized and then another 3 or 4 weeks are required for complete recovery. Recovery having been attained, recurrence of the tetany is commonly not followed by a recurrence of psychic disturbances. Careful neurological examinations in the cases of Greene and Swanson failed to disclose any residual damage to the central nervous system. The facts that the psychosis is of rather early onset in the course of the tetany and that it does not recur with recrudescence of the parathyroid deficiency suggest to the authors that the psychosis may be due to failure of the brain to adjust promptly to the acute chemical changes to which it is subjected.

The marked discrepancy between the frequency of psychosis in tetany in the experience of the recent writers and the rare reports of the condition in other writings obviously suggests that more searching study might bear out Greene and Swanson's conjecture that the association of the two disorders is actually more frequent than is usually recognized. If parathyroid deficiency of the more marked grades actually does have the serious repercussions in the mental sphere that are suggested, the interesting question arises as to what part the parathyroids may play in the mood swings of everyday life. The problem might have some appeal to organically-minded psychologists.

R G H

## RELATION OF THE THYROID GLAND TO BLADDER TONUS

ALTHOUGH several authors have reported atony of the bladder as of frequent occurrence in clinical hypothyroidism, the relationship has apparently not gained wide recognition. In a recent report Sberill and MacKay<sup>1</sup> have called attention to their own experience of the association of the two conditions and have further reported an experimental study of the subject, under controlled conditions.

Three groups of adult male rats, of 8 individuals each were placed on a special adequate diet at the age of 170

<sup>1</sup> *J. Urol.* 46: 34, 1941.

of a 36 year old woman who had experienced slight but continuous mammary secretion since the birth of her only child 16 years previously. The uterus is described as small but the menstrual periods were normal. In this case lactation had apparently been maintained by daily manual manipulation of the breasts.—E. B. A.

HAAGENSEN, C. D., AND H. T. RANDALL.

Production of mammary carcinoma in mice by estrogens. *Arch. Path.* 33: 411. 1942.

The administration of estrone benzoate to pure bred strains of mice produced an increased incidence of breast carcinoma in the male animals to a level which was somewhat higher than in the female controls. It failed to increase the frequency of breast carcinoma in female animals of high cancer strains above the natural frequency in non-treated controls. It did not produce breast carcinoma in male or female mice of the low cancer C57 strain. It did not produce any other type of extramammary malignancy in the treated animals. The authors believe that hereditary factors supersede in importance the effect of estrogen administration on the incidence of breast cancer.—E. von H.

HOLLANDER, L., AND H. R. VOGEL.

Testosterone propionate in treatment of male post-climacteric dermatoses. *Arch. Dermat. & Syph.* 45: 356. 1942.

In 8 cases exhibiting various types of presenile and senile dermatitis inunction treatment with testosterone propionate was attempted. In all patients prompt improvement of the dermatitis was observed although various types of local therapy had been tried without success previously. For this reason the authors recommended the additional use of hormonal treatment in all types of post-climacteric dermatoses.—E. von H.

KOLLER, T.

The estrogenic substance in intra-uterine death. *Helvet. med. Acta.* 8: 639. 1941.

The content of active estrogens increased up to 400% in PU if the latter was stored for weeks or even months. The urinary estrogen content of the same subject increased with the specific gravity of the urine samples. In pregnancy with severe kidney damage, diminution in urinary estrogens occurred prior to intrauterine death of the fetus. In these patients no increase in urinary estrogens was observed before or during parturition. The amount of estrogen is not believed an important factor in induction of parturition.—E. Fischer, in *Bio. Abstracts*.

KRETZSCHMAR, N. R., AND A. C. BARNES.

The extragenital effects of diethylstilbestrol. *Am. J. Obst. Gynec.* 43: 668. 1942.

In general, the effects of diethylstilbestrol on gastrointestinal symptoms, liver functions, body weight, renal system and hematopoietic system in women duplicated those found with the natural estrogens. None of the effects could be considered as representing toxic manifestations of diethylstilbestrol.—C. P.

POTH, D. O., AND S. R. KALISKI.

Estrogen therapy of tinea capitis. *Arch. Dermat. & Syph.* 45: 121. 1942.

The report included the study of 30 consecutive cases which were treated for tinea capitis with estrogens. One group of patients received estrone orally in capsules of 5,000 I.U. per day with additional local treatment of daily application of 1 gm. of ointment containing 5,000 I.U. of estrone. Other patients received diethylstilbestrol in doses of 3 mg. daily in combination with an ointment containing 125,000 I.U. per ounce. A critical analysis of the results showed that only 4 patients failed to obtain a clinical cure and those were ones who discontinued treatment. It was impossible to correlate healing time either with the amount or the type of estrogen administered. The reactions observed during or after treatment consisted in slightly tender enlargement of the breast in 2 male and 2 female patients and 2 cases of vaginal bleeding in girls aged 3 and 5 years. Both reactions subsided promptly after the drug was discontinued.—E. von H.

STURGIS, S. H., AND J. V. MEIGS.

The use of estradiol dipropionate in the treatment of essential dysmenorrhea. *Surg. Gynec. and Abst.* 75: 87. 1942.

The relative value of estradiol dipropionate is compared with other estrogens in their effect on dysmenorrhea. 260 injections were given to 33 patients. 68% of the 130 menses following treatment were painless, 11% of the pain was low, and 20% no change. The advantages of estradiol were minimum of injections and no demonstrable toxic effects.—J. P. P.

SUTRO, C. J., AND L. POMERANTZ.

Changes in osseous tissues of young dogs after prolonged administration of estradiol benzoate. *Arch. Path.* 33: 305. 1942.

The administration of estradiol benzoate to young mongrel dogs did not produce osteosclerosis as was observed in young mice. There was, however, an inhibition of skeletal growth and disturbance of development of the penile bone. These results suggest that other factors besides inhibition of growth may be responsible for the osteosclerosis observed in certain animals after estrogen administration.—E. von H.

TEAGUE, R. S.

Toxicology of the synthetic estrogen diethylstilbestrol and certain related compounds. *J. Pharmacol and Exper. Therap.* 75: 145. 1942.

Daily doses of the various synthetic estrogens as high as 20 mg./kg./day produced no fatalities when administered to rats. All of the compounds produced slight depression of growth and vacuolization of the liver cells which was not fatty degeneration but glycogen accumulation. In addition diethylstilbestrol when given in doses up to 100 mg./kg. daily produced an increase in weight of the liver, adrenal, pituitary and uterus and a decrease in weight of the ovary, testis, seminal vesicle and prostate. The kidney weight was constant.—C. P.

# The Journal of CLINICAL ENDOCRINOLOGY

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## Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone<sup>1</sup>

### [[Gynecomastia]]

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EDWARD C. REIFENSTEIN, JR., M.D. AND  
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THE SYNDROME under discussion begins during adolescence and is characterized by gynecomastia and a very specific type of hypogonadism. This latter is almost entirely in respect to the function of the tubular tissue (germinal epithelium and Sertoli cells) while the function of the Leydig cells (growth of phallus and prostate and of sexual hair) remains relatively normal. Thus one finds bilateral gynecomastia, small testes, aspermatogenesis, evidence of normal to moderately reduced function of the Leydig cells, increased excretion of follicle-stimulating hormone (FSH), and usually a reduced excretion of 17 ketosteroids. During the last 4 years, 7 cases have been observed in the clinics of the Massachusetts General Hospital, studies on these

patients and two additional private patients form the subject of this report.

#### REVIEW OF LITERATURE

Although these cases are not uncommon, few reports are found in the literature, and to our knowledge, no author has grouped them together as a definite clinical entity. Bedor in 1812, according to a later writer (1), described two brothers, 21 and 24 years old, with bilateral gynecomastia and small testes. Around 1840, several English authors (2-5) independently described a soldier, previously normal, who at the age of 53, developed small testes and gynecomastia a few months after trauma to the testes. The reports of this case vary in their details but the sequence of events seems to have been as stated. The development of gynecomastia in a previously normal 22 year old patient a few months after mumps orchitis was reported in 1877 (1). During the last 20 years, there have been several reports (5-9) of cases which possibly fit into this syndrome. Bronstein (10) in 1939 reported the only case, however, in which those hormone studies necessary for the diagnosis were carried out. This concerned a 17-year old negro with gynecomastia of 5 years' duration. The testes were very small and there was azo-

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<sup>1</sup> The expense of these studies was partly defrayed by the Committee for Research in the Problems of Sex of the National Research Council and the Macy Foundation.

<sup>2</sup> Travelling Fellow, Johns Hopkins University Medical School. Read before the Twenty-sixth Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., June 9, 1942.



of a 36 year old woman who had experienced slight but continuous mammary secretion since the birth of her only child 16 years previously. The uterus is described as small but the menstrual periods were normal. In this case lactation had apparently been maintained by daily manual manipulation of the breasts.—E. B. A.

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POTH, D. O., AND S. R. KALISKI.

Estrogen therapy of tinea capitis. *Arch. Dermat. & Syph.* 45: 121. 1942.

The report included the study of 30 consecutive cases which were treated for tinea capitis with estrogens. One group of patients received estrone orally in capsules of 5,000 I.U. per day with additional local treatment of daily application of 1 gm. of ointment containing 5,000 I.U. of estrone. Other patients received diethylstilbestrol in doses of 3 mg. daily in combination with an ointment containing 125,000 I.U. per ounce. A critical analysis of the results showed that only 4 patients failed to obtain a clinical cure and those were ones who discontinued treatment. It was impossible to correlate healing time either with the amount or the type of estrogen administered. The reactions observed during or after treatment consisted in slightly tender enlargement of the breast in 2 male and 2 female patients and 2 cases of vaginal bleeding in girls aged 3 and 5 years. Both reactions subsided promptly after the drug was discontinued.—E. von H.

STURGIS, S. H., AND J. V. MEIGS.

The use of estradiol dipropionate in the treatment of essential dysmenorrhea. *Surg. Gynec. and Abst.* 75: 87. 1942.

The relative value of estradiol dipropionate is compared with other estrogens in their effect on dysmenorrhea. 260 injections were given to 33 patients. 68% of the 130 menses following treatment were painless, 11% of the pain was low, and 20% no change. The advantages of estradiol were minimum of injections and no demonstrable toxic effects.—J. P. P.

SUTRO, C. J., AND L. POMERANTZ.

Changes in osseous tissues of young dogs after prolonged administration of estradiol benzoate. *Arch. Path.* 33: 305. 1942.

The administration of estradiol benzoate to young mongrel dogs did not produce osteosclerosis as was observed in young mice. There was, however, an inhibition of skeletal growth and disturbance of development of the penile bone. These results suggest that other factors besides inhibition of growth may be responsible for the osteosclerosis observed in certain animals after estrogen administration.—E. von H.

TEAGUE, R. S.

Toxicology of the synthetic estrogen diethylstilbestrol and certain related compounds. *J. Pharmacol and Exper. Therap.* 75: 145. 1942.

Daily doses of the various synthetic estrogens as high as 20 mg./kg./day produced no fatalities when administered to rats. All of the compounds produced slight depression of growth and vacuolization of the liver cells which was not fatty degeneration but glycogen accumulation. In addition diethylstilbestrol when given in doses up to 100 mg./kg. daily produced an increase in weight of the liver, adrenal, pituitary and uterus and a decrease in weight of the ovary, testis, seminal vesicle and prostate. The kidney weight was constant.—C. P.

## Abstracts of

# CURRENT CLINICAL LITERATURE

Editor DANIEL A. McGINTY. Collaborators. E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLEY, FRANK A. HARTMAN, R. G. HOSHINO, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PIEPIPER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM

## GONADS

ARNELL, R. E., AND Wm. F. GUERRIERO

Nutritional edema in pregnancy with an analysis of eight severe cases. *Am J Obst. Gynec* 43 467 1942

Nutritional edema results from a protein deficit caused by a deficiency of protein in the diet or by the loss or deficient utilization of ingested protein. It is frequently associated with anemia. Contributory factors include hot weather, overwork, the excessive ingestion of salt water, and the dependent position. In pregnancy, the protein demands of the organism are increased far above normal and cannot be met by a patient suffering from a chronically lowered protein reserve. These 8 patients revealed very marked deficiencies in protein, Fe and vitamins. The treatment, which depends on the etiology, is described.—C. P.

BECKERS, Wm.

Effect of progesterone on uterine contractions. *Am J Obst. Gynec* 43 663 1942

Uterine contractions before and after the subcutaneous administration of synthetic progesterone were studied by means of an intrauterine balloon connected to a mechanical ink recorder which recorded the contractions on a kymograph. Progesterone has no effect upon uterine contractions in the normal ovulatory cycle, either during the follicular or the corpus luteum phase, or upon uterine contractions in threatened abortion or in the puerperium. It has also no effect upon the high-amplitude, hypertonic contractions of primary dysmenorrhea.—C. P.

BURROWS, H., D. H. MACLEOD AND F. L. WARRER

Excretion of ketosteroids in human pregnancy urine in relation to the sex of the fetus. *Nature, London* 149 320 1942

Samples of pregnancy urine were obtained from 20 women and the ketosteroids were established colorimetrically. It was later determined that 14 women were bearing male fetuses and that their average ketosteroid excretion was 26.2 mg per liter. The six women bearing female fetuses had an average ketosteroid excretion of 14.6 mg per liter.—C. P.

ELTON, N. W.

Morphologic variations in adenocarcinoma of the fundus of the uterus, with reference to secretory activity and clinical interpretations. *Am J Clin Path* 12 32 1942

Cyclic changes in the morphological picture of adenocarcinoma of the uterus could be demonstrated in a series of 50 patients. It was found that the cells of the tumor responded to the secretory activity of the ovaries in a way similar to normal endometrium with the exception that the evolution of the secretory stage was slower and did not completely regress in the carcinoma cells. Some cyclic changes were also demonstrated in adenocarcinoma occurring long after the menopause. The prognosis of tumors occurring before the menopause with only menorrhagia as the chief symptom was considerably better than the prognosis of the postmenopausal group, which showed a mortality of 65%.—E. von H.

GESCHICKTER, C. F. AND ELIZABETH BARNES

Factors influencing the development and time of appearance of mammary cancer in the rat in response to estrogen. *Arch Path* 33 334 1942

The authors produced mammary cancer in 202 of 555 albino rats which were treated with estrogens. Over a period of 7 years no spontaneous mammary cancer had been observed in over 5,000 animals of the inbred laboratory stock. The author could demonstrate that all estrogens regardless of the chemical composition or physiological potency would produce mammary cancer in the rat provided that the animal survived the required time. The dose necessary was found to be well beyond the physiological limit, and the treatment must be applied continuously for a period of months. Influencing factors were the dosage, the estrogenic potency, the duration of estrogenic activity, and the method of administration. Simultaneous administration of testosterone or progesterone did not prevent or delay the appearance of mammary cancer. However, estrogenic cancer was partially inhibited by anterior pituitary extract.—E. von H.

GILBERT, B.

Persistent lactation with a note on Chiari and Frommel's disease. *Brit M J* 2 305 1942

The syndrome of puerperal uterovarian atrophy and persistent lactation is discussed and a case is presented

days. A month later the members of one group were thyroidectomized, those of another group were given desiccated thyroid in their diet and the third group were kept as controls. Some three months following, the members of each group were tested for bladder tonus. Each was given an appropriate dose of a radio-opaque iodine compound, following which roentgen-ray photographs were made of the animals in the supine position to show the size of the bladder. The animals of the thyroidectomized group, in general, were found to have a greater bladder volume than did the normal group, whereas the thyroid-fed group showed a slightly smaller volume.

Subsequently a functional test of the tonus was made in each case by anesthetizing the animals, quickly filling the bladders by use of a 20-gauge hypodermic needle

with normal NaCl solution raised to a pressure of 600 mm. of the fluid. The time required for the pressure to fall to 200 mm. was then recorded in seconds. The average for the control group was 2 seconds, the range being from 1 to 5 seconds. In the thyroidectomized group the emptying time was three times as long, averaging 6 seconds and ranging from 3 to 10 seconds. The results in the thyroid-fed group were not remarkable, averaging the same as in the controls.

As to the cause of the flaccidity of the bladder wall in the hypothyroid animals, the authors suggest that depression of nervous responsivity may have been somewhat of a factor, but that it was most likely due chiefly to the depression of metabolism of the muscular tissue of the bladder wall.

R. G. H.



# The Journal of CLINICAL ENDOCRINOLOGY

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## Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone<sup>1</sup>

[Gynecomastia]

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EDWARD C. REIFENSTEIN, JR., M.D. AND  
FULLER ALBRIGHT, M.D.

*From the Medical Service of the Massachusetts General Hospital and the Department of Medicine of the Harvard Medical School, Boston, Massachusetts*

THE SYNDROME under discussion begins during adolescence and is characterized by gynecomastia and a very specific type of hypogonadism. This latter is almost entirely in respect to the function of the tubular tissue (germinal epithelium and Sertoli cells) while the function of the Leydig cells (growth of phallus and prostate and of sexual hair) remains relatively normal. Thus one finds bilateral gynecomastia, small testes, aspermatogenesis, evidence of normal to moderately reduced function of the Leydig cells, increased excretion of follicle-stimulating hormone (FSH), and usually a reduced excretion of 17 ketosteroids. During the last 4 years, 7 cases have been observed in the clinics of the Massachusetts General Hospital, studies on these

patients and two additional private patients form the subject of this report.

### REVIEW OF LITERATURE

Although these cases are not uncommon, few reports are found in the literature, and to our knowledge, no author has grouped them together as a definite clinical entity. Bedor in 1812, according to a later writer (1), described two brothers, 21 and 24 years old, with bilateral gynecomastia and small testes. Around 1840, several English authors (2-5) independently described a soldier, previously normal, who at the age of 53, developed small testes and gynecomastia a few months after trauma to the testes. The reports of this case vary in their details but the sequence of events seems to have been as stated. The development of gynecomastia in a previously normal 22-year old patient a few months after mumps orchitis was reported in 1877 (1). During the last 20 years, there have been several reports (5-9) of cases which possibly fit into this syndrome. Bronstein (10) in 1939 reported the only case, however, in which those hormone studies necessary for the diagnosis were carried out. This concerned a 17 year old negro with gynecomastia of 5 years' duration. The testes were very small and there was azo-

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<sup>1</sup> The expense of these studies was partly defrayed by the Committee for Research in the Problems of Sex of the National Research Council and the Macy Foundation.

<sup>2</sup> Travelling Fellow, Johns Hopkins University Medical School. Read before the Twenty-sixth Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J. June 9, 1942.

ospermia. The phallus was normal, while the other accessory sex organs were small; the amount and distribution of the pubic and axillary hair were normal; the span was 10.5 cm. greater than the height. Estrin excretion was not increased while that of gonadotropin was. The adrenals were normal as shown by roentgenograms after perirenal air injection; the sella turcica was not enlarged. The author did not believe that the gynecomastia was due to hyperestrinism and suggested a pituitary origin.

### Other Causes of Gynecomastia

During puberty, nearly all boys have some breast enlargement (11). Usually slight and often unnoticed, it recedes rapidly as a rule but may become so great

It is probably related to the syndrome under discussion (*vide infra*).

Adrenal cortical tumors of the so-called 'feminizing type' cause gynecomastia (15). With the breast enlargement, there is loss of libido, decrease in secondary sex characteristics, and testicular atrophy. In one case, large quantities of estrin were found in the urine (16); it is quite possible that hyperestrinism is the cause of the gynecomastia in this condition.

Gynecomastia not infrequently occurs with cirrhosis of the liver. Glass, Edmondson, and Soll (17) found atrophic testes in all of their cases and an increased partition of free estrin as opposed to conjugated estrin in the urine. They believe that the cause of the gynecomastia is hyperestrinism, secondary to failure of the liver to prop-

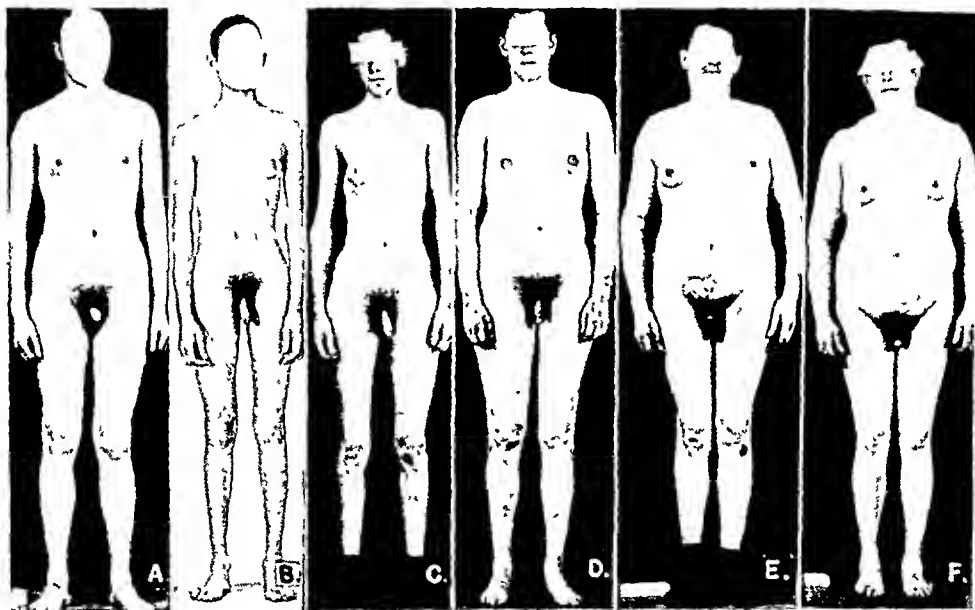


Fig. 1. MASCULINE BODY CONFIGURATIONS and relatively normal development of the accessory sexual organs, except for the breasts. A, case 1; B, case 2; C, case 3; D, case 6, E, case 8, F, case 9.

as to require excision. Strangely enough, the enlargement may increase on one side and regress on the other, often without apparent cause, although trauma is thought to be an important factor.

Gynecomastia is frequently found in association with testicular tumors. Gilbert (12) has recently subdivided these cases into 'choriogenic' and 'physiologic' types. In the former, which occurs with chorionepitheliomata, the breasts may secrete; the areolae are enlarged and pigmented; the estrin and gonadotropin titers of the urine are very high. The gynecomastia is presumably caused by the estrin secreted by the tumor. 'Physiologic' gynecomastia, on the other hand, occurs with other testicular tumors, such as seminomata, teratomata and interstitial cell tumors. In this type, the breasts do not secrete, the areolae are not enlarged or pigmented, and the gonadotropin titer of the urine is only moderately increased. This form of gynecomastia is presumably secondary to atrophy of the remaining testis, as it frequently occurs after roentgen ray treatment has been given post-operatively (13, 14).

erly metabolize estrin. No testicular biopsies were made in their cases.

Gynecomastia rarely occurs with pituitary tumors (18, 19), hyperthyroidism (20) and after prostatectomy (21).

### Clinical Findings

The 9 cases here reported whose histories are outlined in the appendix varied in age from 17 to 38 years; all were white except one negro. Three had an asthenic habitus; 4 were somewhat obese; 2 had a normal build. All of the patients were strong and had good muscular development (fig. 1).

Early development was normal in every case. None of the patients had undescended testes. There was no history of orchitis, although most of the patients had had mumps. Puberty started between the ages of 12 and 14 in each case.

The gynecomastia was bilateral in every case; (fig. 2 and 3); it was first noticed by the patients from

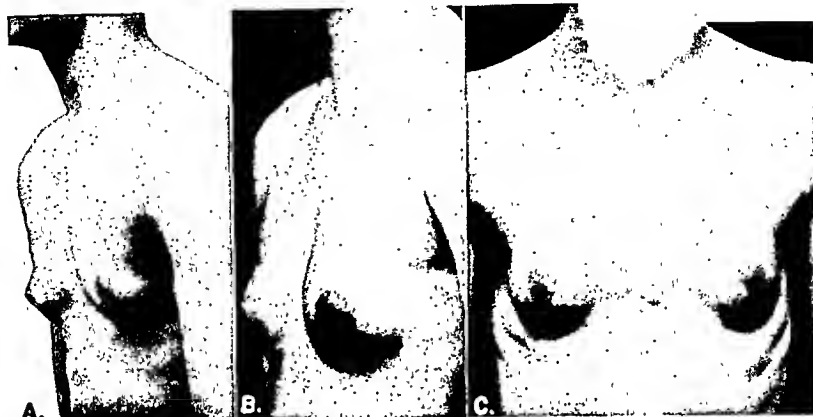


Fig. 2. A, case 2; B, case 6; C, case 3.

1 to 6 years after puberty began. Those patients who observed breast enlargement during the first few years after the onset of puberty stated that the breasts slowly increased in size over a period of several years and then remained stationary; those who did not notice the enlargement until 4 to 6 years after the onset of puberty, on the other hand, said that there was no further change during the subsequent years. The gynecomastia was marked in 7 cases and moderate in 2. The breasts resembled those of the adolescent female, with some areolar enlargement and very little increase in pigmentation. No secretion was expressed in any case, and in only two cases was tenderness present. This was unilateral and started after manual stimulation in one case.

The testes were very small, measuring about  $1.5 \times 1.0 \times 0.5$  cm. There was no difference between the two sides and there was very little variation among cases. The testes were normal as to firmness and sensitivity to pressure. Those patients who had observed the size of their testes stated that they had always been small.

Three of the patients had no semen, i.e., aspermia while the remaining 6 had ejaculations. Semen examination showed azoospermia in the 4 cases in which this test was made. Sterility was the chief complaint of 3 patients.

Eight of the 9 cases had well developed accessory sexual organs, and clinically all 8 patients had relatively good Leydig function, although the younger patients appeared immature for their age. Only case 5 had obviously diminished Leydig function. He, at the age of 28, had a high-pitched voice, a small larynx, sparse beard, small phallus and small prostate. He had

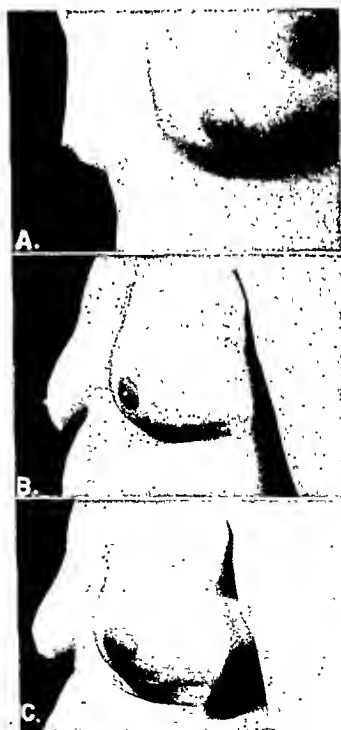


Fig. 3. A, case 1; B, case 8; C, case 9

erections but no ejaculations and never attempted intercourse, although he was attracted to the opposite sex.

Axillary, pubic and perianal hair growth were essentially normal in these patients, and several of the older ones had definite recession of the hair above the temples, an indication of good Leydig function (22). The 5 younger patients, aged 17, 18, 22, 24, and 28, respectively, did not shave. Two of the 4 older ones had scanty beards localized to the chin and upper lip which required shaving only once or twice a week. In one patient, however, this was a familial characteristic. Body hair was scanty in all of the 7 patients

and showed no consistent deviation from normal. There was no clinical evidence of liver disease in any of the patients; in cases 2 and 5, the bromsulphalein test, the cephalin flocculation test, the serum Van den Bergh reaction, the serum proteins, and the A/G ratios were normal.

Hormonal Findings

*Follicle-stimulating hormone.* All of the patients excreted excessive amounts of the pituitary follicle-stimulating hormone (FSH) in the urine. By our assay method (23), which is a modification of the alcohol precipitation method of Zondek, a normal male rarely

TABLE 1. CLINICAL DATA ON PATIENTS WITH GYNECOMASTIA

| Case no. | Age, yr. | Onset of Puberty, yr. | Gyneco- mastia First Noted, age, | Bone Age, yr. | Height, cm. | Span, cm. | Highest FSH Determinations |           |                    |           | 17-Ketosteroids, mg./24 hr. |       |      | Remarks   |
|----------|----------|-----------------------|----------------------------------|---------------|-------------|-----------|----------------------------|-----------|--------------------|-----------|-----------------------------|-------|------|---|
|          |          |                       |                                  |               |             |           | Mouse Units/100 cc.        |           | Mouse Units/24 hr. |           | Low                         | High  | Ave. |   |
|          |          |                       |                                  |               |             |           | Greater than               | Less than | Greater than       | Less than |                             |       |      |   |
| 1        | 17       | 13                    | 13                               | Normal        | 181.1       | 185.0     | 30                         | 50        | 235                | 350       | 5.6                         | 8.7   | 7.2  | Negro   |
| 2        | 18       | 14                    | 14                               | Normal        | 170.7       | 180.2     | 100                        | 150       | 640                | 840       |                             |       | *    |   |
| 3        | 22       | 14                    | 17                               | Normal        | 175.4       | 178.0     | 50                         | 80        | 150                | 248       | 6.0                         | 9.0   | 7.2  |   |
| 4        | 24       | 14                    | 18                               | Normal        | 182.2       | 183.5     | 80                         | 100       |                    |           | 1                           | Assay | 4.8  |   |
| 5        | 28       | 14                    | 18                               | Delayed       | 177.0       | 181.5     | 50                         | 100       |                    |           | 3.9                         | 5.2   | 4.6  |   |
| 6        | 30       | 13                    | 14                               | Normal        | 183.5       | 184.2     | 50                         | 80        | 200                | 320       | 12.6                        | 13.5  | 13.1 | Hysteria<br>Definite hypo-<br>leydigism<br>Narcolepsy.<br>Renal lithiasis |
| 7        | 33       | 13                    | 16                               | Normal        | 182.2       | 184.2     | 30                         | 50        | 270                | 450       | 7.2                         | 13.2  | 9.6  |   |
| 8        | 35       | 14                    | 16                               |               | 177.5       | 178.0     | 30                         | 50        | 330                | 455       | 9.6                         | 11.2  | 10.3 |   |
| 9        | 38       | 12                    | 18                               |               | 171.6       | 175.5     | 50                         | 80        |                    |           | 7.9                         | 10.5  | 9.2  |   |
|          |          |                       |                                  |               |             |           |                            |           |                    |           |                             |       |      | Chronic cystic disease of right lung                                      |

\* The pre-treatment assays of 1.2 and 2.4 mg. averaging 1.8 mg. per 24 hr. are thought to be due to faulty technique, and are not included. Later assays, after 4 to 6 weeks without treatment, ranged from 4.3 to 9.0 mg., with an average of 5.7 mg. per 24 hr.

with abnormal beards while the 2 with heavy beards ad abundant body hair.

Bone age (table 1) was determined in all of the ounger patients and was definitely delayed in only ne patient, case 5. At the age of 21 the epiphyses f the radius and ulna were open, indicating a delay of 3 years in bone age; however, at the age of 28, without treatment, these epiphyses were closed. The span exceeded the height in every case, however; where this discrepancy was marked, circa 4 to 5 cm., there probably had been some delayed epiphyseal union.

There was questionable serological evidence of syphilis in only one patient, case 2; the Hinton test was negative in the others. Roentgenograms of the sella turcica were uniformly normal. Perirenal air injections were performed on 2 patients and the findings were normal. Glucose tolerance tests were made on 3 patients and revealed nothing remarkable. Basal metabolic rates were obtained on 6 patients

excretes 10 mouse units of FSH per 100 cc. of concentrated first morning urine. These patients uniformly excreted more than 30 M.U. per 100 cc., and 5 of the 8 have excreted more than 50 M.U. per 100 cc. (table 1). In the table, FSH excretion levels in some cases are also recorded in M.U. per 24 hr. Calculated on this basis, the excretion levels were also much above normal. Such data required very accurate collections of urine which were not obtainable in all cases. These high levels of FSH excretion are comparable to the levels found in castrates and their significance will be discussed later.

*17-Ketosteroids.* The urinary excretion of 17-ketosteroids varied from relatively normal to definitely subnormal levels. Thus, in a small series of normal males between the ages of 20 and 40, values from 8.1 to 22.6 with an average of 13.8 mg. per 24 hours were obtained in this laboratory (24). As can be seen from the table, the range in this series of 9 patients was from 3.9 to 13.5 with an average of 8.3 mg. per

24 hr By and large, there was a parallelism between the degree of hypopogonism, as judged clinically, and the lowering of the 17 ketosteroid excretion

**Estrin assays** Estrin assays were made on case 2 by Drs C V and O W Smith in the Ferring Research Laboratory of the Free Hospital for Women. They found no evidence of increased excretion of either estrin or estrin breakdown products, the levels being about the same as those found in menopausal women and in the only normal male they had studied. Estrin assay on case 8 made in our laboratory in 1938 was negative for 10 R U per 24 hr

### Histological Findings

**Testis** Testicular biopsies were obtained from 7 patients and showed varying degrees of the same lesion. This involved the tubules and in its most advanced state consisted of hyalinization of all the tubular elements (fig 4, 5). This hyaline tissue stained pink with eosin and like collagen with phosphotungstic acid and aniline blue. Stains for amyloid were negative. In many of the biopsy tissues, fine granules were seen in the hyaline tissue, these granules did not stain like collagen, however, and their nature is obscure, they seem to be part of the atrophic or degenerative process. This lesion of the tubules is not the 'peritubular fibrosis' described by Charny and Meranze (25), and there was no evidence of an inflammatory process in any of the biopsies. The less advanced lesions showed partial hyalinization with impaired spermatogenesis (fig 4, B), in no instance was normal spermatogenesis present.

The interstitial cells were numerous in all of the biopsies and in most cases the Leydig cells seemed, at first, more numerous than could be accounted for by the atrophy and shrinkage of the seminiferous tubules. Indeed, the diagnosis 'hyperplasia of the interstitial cells' was considered by the pathologist. When one calculates the size of these small testes, however, it seems probable that simple shrinkage can account for the apparent increase in the number of interstitial cells. A testis measuring  $1.5 \times 1.0 \times 0.5$  cm

equals approximately 0.75 cc of tissue, while a normal testis measuring  $5.0 \times 3.0 \times 2.0$  cm equals approximately 30 cc of tissue. In other words, one would expect the interstitial cells to be 40 times as numerous as in the normal testis.



Fig 4 TESTICULAR BIOPSY TISSUE A case 6 B case 7 a Leydig cells b completely hyalinized tubules c partially hyalinized tubule. Note that the Leydig cells in A almost suggest adenoma formation.

**Breast** The breast tissue was examined microscopically in 4 patients and showed some hyperplasia of the duct epithelium and marked proliferation of the periductal connective tissue (fig 6, A and B). These findings are definitely different from the effects produced by estrin therapy in an elderly male (fig 6, C), there the ratio of ductal to periductal hyperplasia was greater.

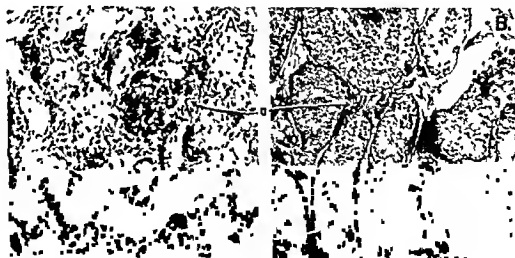


Fig 5 TESTICULAR BIOPSY TISSUE A case 1 B normal a Leydig cells b completely hyalinized tubule c normal tubule



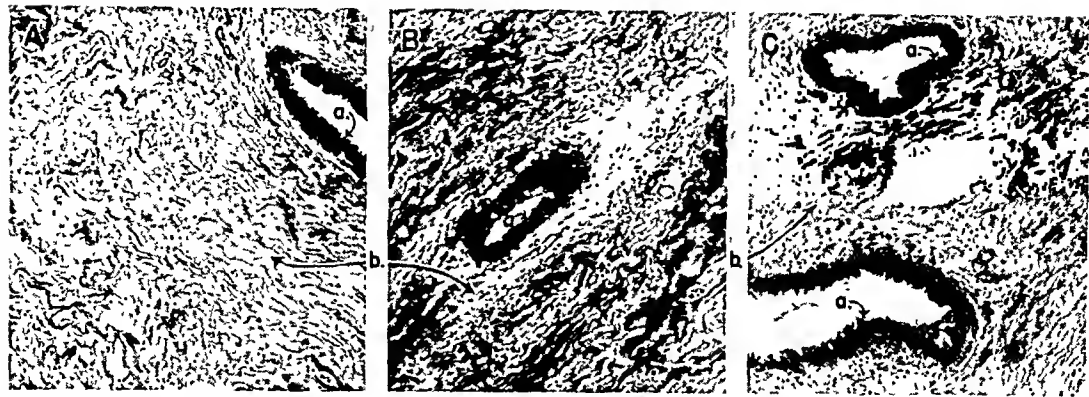


Fig. 6. BREAST TISSUE. A, case 2; B, case 6; C, M. G. H. 334479, a 78-year-old male with estrin-induced gynecomastia. In A and B there is only moderate ductal hyperplasia (a), with marked proliferation of the periductal connective tissue (b); in C, the ductal hyperplasia (a) is more marked and the periductal connective tissue (b) is less dense.

Pathological Physiology

*Significance of increased FSH excretion.* Since the significance of an increased FSH excretion has been more thoroughly studied in the female, it may be well for purposes of orientation to consider first the hormonal patterns in the normal and in the gonadec-

tomized female. In figure 7, A the part of the anterior pituitary under consideration is divided into 2 compartments, one for FSH and one for the luteinizing hormone (LH). In this and subsequent diagrams, stimulating influences are indicated by arrows with solid heads while inhibiting influences are indicated by arrows with open heads. It will be noted that FSH stimulates the ovary to produce estrin (E); that estrin in turn inhibits FSH production and stimulates LH production. The evidence for these statements is discussed in a previous paper (26). To be absolutely accurate it is still a question whether estrin stimulates LH or luteotropin or both; this uncertainty is indicated by the question mark after LH in the second compartment. For the present argument this is immaterial. The important fact is that estrin stimulates some hormone of the pituitary which in turn stimulates the ovary to produce more progesterin (P). Finally, it will be noted that progesterin inhibits LH production (27).

Figure 7, B is constructed in a similar manner to show the changes in the hormonal pattern resulting from castration. Estrin is absent and consequently there is no inhibition of FSH production. There results an overproduction of FSH and large quantities are excreted in the urine. It will be noted that LH production is depicted as decreased. Whether this is true in the gonadectomized female probably depends on whether the loss of the stimulating effect of estrin on LH overbalances the loss of the inhibiting effect of progesterin on LH.

Before describing the hormonal pattern in the syndrome under discussion (fig. 8, C) it will be helpful to outline these patterns in the normal and in the gonadectomized male (fig. 8, A and B). These diagrams follow the same general scheme as those in figure 7. It will be noted that FSH stimulates the tubules (T) to produce spermatozoa (S) (28) and an 'X-hormone.' The arguments for the existence of this X-hormone and for its actions will be enumerated

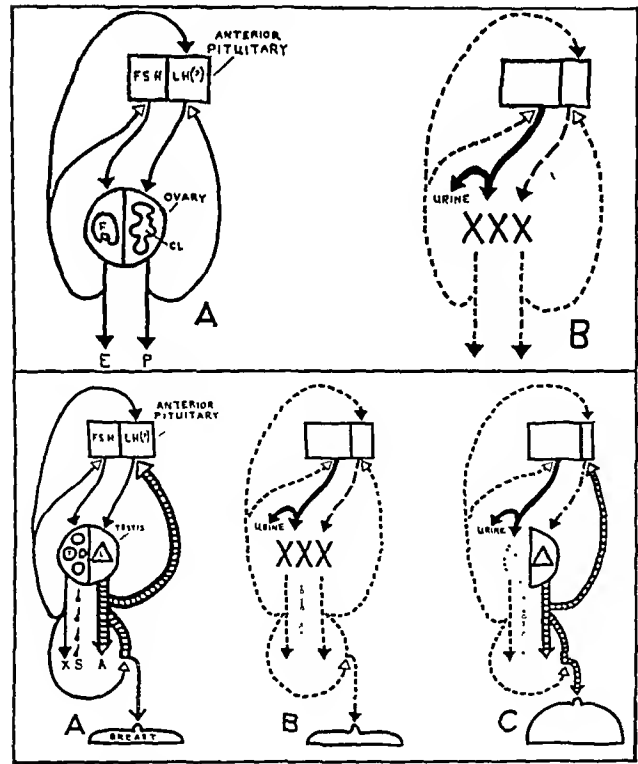


Fig. 7. SCHEMATIC DRAWING REPRESENTING HORMONAL PATTERNS in normal female (A) and gonadectomized female (B). Finely dotted line indicates absence of hormone; broken line indicates decreased production of hormone. For discussion, see text.

Fig. 8. SCHEMATIC DRAWING REPRESENTING HORMONAL PATTERNS in normal male (A), gonadectomized male (B), and syndrome under discussion (C). Finely dotted line indicates absence of hormone; dot-dash line indicates markedly decreased production of hormone; broken line indicates decreased production of hormone. For discussion, see text.

below. It will be noted further that the X-hormone is analogous to estrin in that it inhibits FSH production and stimulates LH production. LH stimulates the Leydig cells (L) to produce androgen (A) (28); androgen, like progesterin, inhibits LH production. The discussion of the effect of these various hormones on the breast is reserved for a later section.

In figure 8, B it should be emphasized that it is primarily lack of the inhibiting effect of the X-hormone on FSH, and not lack of androgen, that leads to overproduction of FSH. The situation, therefore, is depicted as exactly analogous to that in a gonadectomized female; the arguments for this rendering will be discussed below.

Turning to the hormonal pattern of the syndrome under discussion (fig. 8, C) one notes first that the tubular part of the testis is non-functioning while the part which has to do with Leydig cells is relatively normal (cf. biopsies, fig. 4, 5). The increased FSH production is the result of lack of X-hormone with its inhibiting effect. LH production is less than normal because of lack of stimulation by the X-hormone, it is even less than that in the male castrate (fig. 8, B) because the inhibiting effect of androgen is partially retained. Androgen production, while less than normal, is still present.

The description of the hormonal pattern has been expressed in rather dogmatic terms. The argument will now be taken up point by point.

*Evidence for a second or X-hormone (inhibin) of the testis.* The first and weakest argument for the presence of a second testicular hormone is by analogy with the female. There FSH facilitates production not only of the germ cells but of a hormone, estrin, as well; it would seem, therefore, in the male that FSH might be concerned with the production of a hormone in addition to the germ cells.

The literature, furthermore, contains considerable evidence in favor of the existence of such a hormone. Mottram and Cramer (29) in 1923 found castration cells in the pituitaries of adult male rats that had received roentgen ray treatment to the testes. This treatment resulted in atrophy of the seminiferous tubules but preservation of the interstitial cells and accessory sex organs. Witschi, Levine and Hill (30) in 1932 found that female rats in parabiosis with such male rats develop continuous estrus. This finding is good evidence for increased FSH production. Martins and Rocha (31) in 1931 reported on parabiotic union of castrated males with infantile normal females. When the males were untreated, precocious puberty resulted in the females, however, when the males were treated with testicular extracts or implants, precocious puberty did not occur in the females, in spite of the fact that the extracts did not contain androgen as judged by the accessory sex

organs of the treated males. McCullagh and Walsh (32) confirmed this work and coined the word 'inhibin' for the water-soluble, non-androgenic hormone of the testis. They showed furthermore that inhibin caused regression of the prostate and seminal vesicles in normal rats. This finding was confirmed by Vidgoff, Hill, Vehrs, and Kubin (33) in 1939 and brings to mind Huggins' studies (34) on the effect of estrin (a hormone closely related to inhibin) on the prostates of dogs. Nelson (35) in 1934 studied rats made cryptorchid by operation and found castration cells in the pituitaries after 75 days, while 240 days were required for atrophy of the seminal vesicles and 400 days for the prostate. Since the tubules in cryptorchid males degenerate long before the interstitial cells, these time relationships suggest that the occurrence of castration cells is correlated with the tubules while the atrophy of the seminal vesicles and prostate is correlated with the interstitial cells. Indeed, the atrophy of the interstitial cells may very well be due to lack of stimulation of LH by inhibin (fig. 8, A). There are, of course, other interpretations (vide *infra*).

The clinical findings in certain cases of arrhenoblastoma of the ovary suggest that these tumors produce some hormone other than androgen. Thus, in one (M.G.H. 176118) of the 4 cases studied in this clinic there were no masculinizing effects, merely amenorrhea. The amenorrhea in this case disappeared shortly after removal of the tumor. Although complete hormonal studies are lacking, it would seem in retrospect that the finding could best be explained on the supposition that the tumor in this case primarily produced inhibin. Indeed, in the 2 cases with definitely masculinizing symptoms, (M.G.H. 174105 and 245129) the 17-ketosteroid excretion levels were not elevated which suggests that even in these cases the amenorrhea might have resulted from excessive production of inhibin.

The authors believe that the findings in the syndrome here described offer strong evidence in favor of the dual hormonal theory of testis physiology. Here nature has apparently produced destruction of one part of the testis while sparing the other. In the face of only slight if any hypop Leydigism, one encounters FSH excretion of the order of magnitude of that found in castrates. Thus case 6, with perfectly normal development of the accessory sexual organs, aside from the gynecomastia, and with a relatively normal 17 ketosteroid output, excreted more than 200 mU of FSH per 24 hours. Furthermore, the very fact that gynecomastia occurs in this syndrome while it does not occur after castration is further evidence that some hormone other than androgen is involved.

*Evidence against a second or X-hormone of the testis.* The fact that testosterone inhibits FSH pro-

duction has led to an alternate theory, the monohormonal theory. Thus, Nelson (35) points out that the sequellae of experimental cryptorchidism in rats discussed above disappear under testosterone therapy in the reverse order in which they occur, and thinks that everything can be explained on the basis of dosages. If this interpretation were extended to the syndrome here presented, the argument would be that the patients were suffering from a mild degree of hypoleydigism, not sufficient to affect the genital organs but sufficient to cause increased FSH production. A point perhaps against this argument is that case 2 with the highest FSH excretion did not have the greatest degree of hypoleydigism.

In rebuttal, the authors point out that the histological picture of hyalinized tubules in the presence of normal or hypertrophic interstitial cells make it difficult to believe that one is dealing primarily with an underfunction of the androgen-producing elements. Moreover, the fact that so much more testosterone is required to prevent development of castration cells than to affect seminal vesicles and prostate suggest to the authors that inhibition of formation of castration cells is not a physiological function of testosterone. It seems not impossible to the authors, furthermore, that the inhibitory effect of testosterone on FSH production may very well be connected with the observation that if testosterone is administered to eunuchoids and castrated females, the excretion of estrin is increased (36-39). It is very possible that testosterone is converted into estrin which inhibits FSH.

*Cause of the decreased 17-ketosteroid excretion.* The 17-ketosteroids in the male are produced in two places, the adrenal cortex and the cells of Leydig (24). In the syndrome here described the values vary from apparently normal to definitely subnormal. Since the 17-ketosteroid excretion level varies considerably among normal individuals it can not be said that any one of the patients here reported had an excretion level as high as it would have been without the disease. The authors suggest, as an explanation for this lowering, a lack of X-hormone to stimulate both the Leydig cells and possibly those cells of the adrenal cortex which produce 17-ketosteroids. The above chain is thoroughly discussed in the paper previously referred to (26).

*Cause of the gynecomastia.* The most puzzling part of the whole syndrome is the gynecomastia. One first considers the possibility of too much estrin. Against this possibility are a), the presence of high FSH excretion, b), the fact that the histological changes in the breast are more periductal than ductal hyperplasia, and c), the fact that no increased estrin excretion was found in case 2 by Drs. G. V. and O. W. Smith or in case 8 in our laboratory.

One might consider the uncommon causes of gynecomastia such as adrenal hyperfunction, pituitary tumors and testicular tumors. No evidence in favor of these has been found. Progesterone was administered to cases 1 and 2 with the thought that this would be followed by lactation if excess of prolactin had anything to do with the etiology. Lactation did not occur.

Could the gynecomastia be due to testosterone? It has been shown that testosterone stimulates breast tissue in normal and castrated female and male rats (40). Gynecomastia is not uncommon in eunuchoid patients treated with testosterone (41); it became so marked in one of our patients as to require excision. The excised breasts in this particular case showed the same histological picture seen in this syndrome. But testosterone can not be the only factor, since if this were so, normal males would have gynecomastia.

After all, the pathology indicates isoleydigism accompanied by hypoinhibinism. The authors bring up for discussion the hypothesis that for the production of this type of gynecomastia, two conditions must be fulfilled. a), presence of androgen, b), absence of inhibin. One is reminded of Huggins' observations on the prostate of dogs in which he found that testosterone causes growth and estrin prevents such growth (34). Could it not be that in the male breast testosterone causes growth and inhibin prevents this growth? If such were the case the castrate would not develop gynecomastia because of the lack of testosterone (fig. 8, B), the normal would not because of the presence of inhibin (fig. 8, A), while the patients with this syndrome would, since they have testosterone but no inhibin (fig. 8, C). To be sure, Hamilton (42) has found that testosterone therapy does not always cause gynecomastia in male castrates. Since these cases were all adults, it may very well be that a third condition need be fulfilled, namely that the patient be growing at the time of the hormonal imbalance.

To recapitulate, the selective lesion of the seminiferous tubules results not only in aspermatogenesis but also in lack of X-hormone (inhibin); lack of X-hormone leads not only to increased FSH production but to decreased LH production as well; consequently the intact Leydig cells produce somewhat less androgen than normally; the androgen produced acts on the breast during puberty in the absence of X-hormone to cause gynecomastia.

#### *Etiology*

Nothing has been found in these patients to explain the testicular lesion. There is no evidence of any inflammatory disease clinically or histologically. An obstructive lesion of the vas deferens seems most

unlikely since histological studies of the testes in cases of known obstruction do not resemble at all the histological picture seen here (43). Furthermore an epididymal biopsy from case 6 contained normal tissue. The changes, moreover, are not those seen with lack of gonadotropic hormones, as in pituitary dwarfs in which one finds rudimentary tubules with aspermatogenesis but no hyalinization. One is left with the conclusion that the lesion is a degenerative one of unknown etiology, starting early in life.

#### Treatment

It is very improbable that the gynecomastia is reversible. Testosterone propionate and progesterone have been tried without success; estradiol dipropionate caused further enlargement. Surgical removal of the breast is recommended for cosmetic reasons, and if carefully done is an exceedingly satisfactory procedure.

From the histological findings, it seems unlikely that anything can be done to correct the aspermatogenesis. The high FSH titers in the urine demonstrate that these patients are over-producing FSH in an effort to stimulate spermatogenesis. Therefore, therapy with gonadotropins is probably illogical.

For those patients in this group who are suffering from hypogonadism, testosterone therapy is probably indicated. Chorionic gonadotropin therapy by stimulating the interstitial cells might conceivably be used to produce the same results as testosterone; it has not been tried by the authors in the series of cases here reported.

#### SUMMARY OF FACTS

1. Nine cases are presented of a syndrome characterized by gynecomastia, and small testes with aspermatogenesis but without hypogonadism.

2. The follicle-stimulating hormone (FSH) excretion in the urine is increased to a degree comparable to that found in castrates.

3. Estrin excretion was studied in two cases and found not to be increased.

4. The 17-ketosteroid excretion level and the development of the accessory sexual organs vary from apparently normal to definitely subnormal.

5. Testicular biopsies were obtained on 7 patients and showed hyalinization of the seminiferous tubules and normal appearing interstitial cells.

6. Breast tissue was examined on 4 patients and showed some ductal hyperplasia with marked proliferation of the periductal connective tissue.

#### Interpretations

1. These studies support the point of view that the testis produces two hormones; a), androgen from the Leydig cells, and b), X-hormone (inhibin) from the tubules.

2. Inhibin is analogous and probably very similar to estrin.

3. The increased FSH excretion which is found in certain types of hypogonadism depends primarily upon lack of inhibin and only to a lesser degree upon lack of androgen; indeed the action of testosterone in inhibiting FSH may depend upon its conversion into estrin.

4. The gynecomastia is not due to hyperestrinism; it is not due to androgen alone; it may be due to the combination of androgen and lack of inhibin.

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#### CASE HISTORIES

In the following case abstracts, the data for the FSH tests and the 17-ketosteroid excretion levels are omitted, as they are recorded in table 1.

**Case 1** (fig. 1, A), R.R. (M.G.H. 344755), a 17-year-old white schoolboy, was seen in March, 1942, complaining that he had been rejected by the Navy because of small testes. His general health was excellent. He had mumps at 2 years of age without orchitis. At 10 or 11, he suffered from trauma of the scrotum, but there was no swelling or pain. Since that time, he noticed that the testes were small. Puberty began at 13 and progressed normally. He had normal erections, masturbated occasionally, but had no ejaculations or nocturnal emissions. He never shaved, but his voice had changed. Shortly after the onset of puberty, he noted enlargement of the breasts which slowly increased for a few years (fig. 3, A). The enlargement was never enough to cause him embarrassment.

Examination showed a well developed, muscular boy with mild acne, with somewhat narrow shoulders and rather wide hips. The span was 4.0 cm. greater than the height. Axillary and facial hair were scanty, but pubic hair was normal. The voice was deep and the larynx showed normal masculine enlargement. The breasts were moderately and equally enlarged, non-tender, and no secretion could be expressed. The phallus and scrotum were well developed; the prostate was slightly small. The testes were very small, equal in size, firm and normally sensitive.

Hinton test for syphilis was negative. Roentgenograms showed a normal bone age. Biopsy of the right testis showed complete hyalinization of the tubules and apparently normal interstitial cells (fig. 5, A). Estradiol dipropionate, 5 mg. intramuscularly every 5 days, caused tenderness and further enlargement of both breasts after 4 injections.

**Case 2** (fig. 1, B), G.B. (M.G.H. 147829), an 18-year-old negro, was admitted in September, 1941, complaining of gynecomastia. His general health was always good; early development was normal. He had measles, chicken

pox, scarlet fever and pneumonia in childhood, but not mumps. At the age of 10, he was seen in another hospital because of a coarse tremor of both hands. Wassermann reaction and Kolmer tests were positive, while the Kahn test was negative. He received no antisiphilic treatment, and the tremor ceased after a few weeks. Five and 7 years later, Hinton tests were negative; there was never any clinical evidence of syphilis. He had never had orchitis or testicular trauma, and had never noticed the size of the testes. Puberty began at 14 and progressed fairly normally. He masturbated occasionally with pleasurable sensation, but without ejaculations; he had erections but no nocturnal emissions. Within a year of the onset of puberty, he noticed enlargement of the breasts and this increased slowly during the next few years (fig. 2, A).

Examination showed a well developed, thin boy who appeared younger than his stated age. The span was 9.5 cm. greater than the height. Axillary, pubic and perianal hair were normal; he had no beard. The voice was deep and the larynx was normal in size. The breasts were quite large, resembling those of a pubertal girl, non-tender and no secretion could be expressed. The phallus was quite large; the scrotum was well developed; the prostate about normal in size. The testes were extremely small and equal in size. There was a small hydrocele on the right.

Hinton test was negative on three occasions and doubtful on one. Estrin essays: 15 R.U./24 hr. (equivalent to 7.5 micrograms of estrone/24 hr.) before zinc hydrolysis; 42 R.U./24 hr. after zinc hydrolysis (Drs. G. V. and O. W. Smith). The bromsulphalein, cephalin flocculation and Van den Bergh tests were all normal, as was the serum protein content of the blood. Glucose and insulin tolerance tests were entirely normal. Roentgen-ray examination showed a normal sella turcica, normal bone age, and normal adrenals after air injection. Biopsy of the right testis showed marked impairment of spermatogenesis with hyalinization of many seminiferous tubules while the interstitial cells were well preserved.

This patient was treated with large doses of testosterone propionate, progesterone, and pregnenolone without grossly altering the breasts or testes. In June, 1942, both breasts were excised and showed proliferation of the ductal epithelium with marked proliferation of the periductal connective tissue (fig. 6, A). Hinton test was again negative.

*Case 3* (fig. 1, C), F.S. (M.G.H. 119837), a 22-year-old single white laborer, was seen in March, 1940, complaining of gynecomastia. His general health was always fairly good, but he had always been thin. He had mumps without orchitis. There was no history of any previous disease of the testes; the patient thought they were 'always small.' At 13, he had an operation on the left eye for strabismus. For many years he had had severe dental caries and pyorrhea. Puberty began at 14 and progressed normally. At 17 he first noticed enlargement of the breasts and this increased slowly for several years (fig. 2, C). There was no further enlargement during the 2 years that he was under observation. He had satisfactory erections, intercourse and ejaculations.

Examination showed a tall, thin man with large hands and feet who appeared younger than the stated age. The

span was 2.5 cm. greater than the height. Axillary and pubic hair was normal, but the beard was scanty. The voice was a little high-pitched, but the larynx was of normal size. The breasts were markedly enlarged, resembling those of an adolescent girl; they were not tender and no secretion could be expressed. The phallus, prostate, and scrotum were normally developed. The testes were extremely small, but the epididymes were well developed.

Hinton test was negative. Biopsy of the left testis showed complete hyalinization of the seminiferous tubules and normal looking interstitial cells. This patient was treated for several months with large doses of testosterone propionate without any effect on the breasts or testes.

*Case 4*, B.C., (private patient of Dr. J. O. W. Rash), a 24-year-old unmarried white laborer, complained of gynecomastia and small testes. He was always robust and was somewhat obese from the age of 10 to 15 years. He had measles at 9 and influenza 3 or 4 times in childhood. There was no history of mumps orchitis, or trauma to the testes. From 8 to 12, he had frequent attacks of syncope, with loss of memory, lasting 30 to 45 minutes, without epileptiform symptoms. Puberty began at 12 and progressed fairly normally, except that the voice never changed and he had never shaved. Intercourse was unsatisfactory; he had ejaculations, but no nocturnal emissions. Glasses were prescribed at 10 because of poor vision in the right eye; at 17 he complained of increased loss of vision with blurring and was admitted to the Johns Hopkins Hospital. It was noted then that he had gynecomastia and small testes. Ventriculograms revealed no abnormality; visual fields showed a binasal hemianopsia, which was thought to be functional in origin. The gynecomastia was first noticed by the patient at the age of 18 and has not progressed since that time.

Examination showed a rather obese, unintelligent, timid, self-conscious man with wide hips and slightly narrow shoulders. The span was not significantly greater than the height. The axillary and perianal hair were scanty; the pubic hair was normal; the beard was scanty. The voice was high-pitched. There was complete loss of vision in the right nasal quadrants; the optic fundi were normal. The breasts were greatly enlarged. The phallus was normal in size, with a slight degree of hypospadias; the prostate was somewhat small. The testes were very small, equal in size and normal in consistency. Roentgenograms showed a normal bone age. No semen specimen or testicular biopsy could be obtained.

*Case 5*, W.J. (M.G.H. 296608), a 28-year-old feeble-minded white houseboy was admitted in April, 1934, at the age of 21 because of gynecomastia. He was an inmate of a State Institution and during the few months before admission manual manipulation resulted in swelling and pain of the right breast. His general health was fairly good. He had had influenza on two occasions, but did not remember having mumps. He never had orchitis or trauma to the testes, and thought the testes were 'always small.' Puberty began at 15, but the voice did not change, and he never had nocturnal emissions. He had erections but never attempted intercourse and masturbated only a few times, with no ejaculations. At about 18, he first noticed

breast enlargement and this continued for the next few years. The breasts were never painful or tender until the months before admission (*vide supra*).

Examination showed a tall immature boy with narrow sloping shoulders and wide hips. The height was 2.0 m greater than the span. Axillary and pubic hair were normal. The voice was high pitched. Both breasts were markedly enlarged, the right more than the left, the right breast was slightly tender to palpation. The phallus and scrotum were fairly well developed while the prostate was small. The testes were very small.

The FSH test was positive for at least 8 M U per 100 cc. The glucose tolerance test was not remarkable. Roentgenograms showed a normal sella turcica, the epiphyses of the radius and ulna were open, indicating a 3 year delay in bone age. Basal metabolic determinations were -4, -5 and +9. Both breasts were amputated and showed hyperplasia of the ductal epithelium and proliferation of the periductal connective tissue.

The patient was again seen in November, 1941, at the age of 28. The voice had not changed and he had not shaved. He had only occasional erections, no ejaculations and had not attempted intercourse.

Examination showed a tall, immature boy, who was quite thin. The span was 5.0 m greater than the height. Axillary and pubic hair were normal, facial hair was sparse. The voice was high pitched and the larynx did not show normal masculine development. No breast tissue could be felt under the scars of the amputations. The phallus and scrotum were still only fairly well developed and the prostate was small. The testes were extremely small. There was a hydrocele on the left.

Hinton test was negative. Roentgenograms showed that the epiphyses of the radius and ulna had closed. The bromsulphalein cephalin flocculation, and Van den Bergh tests were normal as were the serum proteins. Biopsy of the right testis showed marked impairment of spermatogenesis with hyalinization of most of the tubules and normal appearing interstitial cells.

Case 6 (fig 1, D) LB (MGH 141135), a 30-year-old unmarried mechanic, was seen in May, 1942, complaining of small testes and gynecomastia. His general health was always good. He had never had mumps and there was no history of orchitis. The testes were "always small." At 11 and again at 30, he had pneumonia without complications. Puberty began at 13 and progressed normally. At 14 he first noticed lumps in both breasts which were slightly tender. The breasts slowly increased in size, and he could not remember when they ceased enlarging, but they had remained stationary for at least 6 years (fig 2, B). At 28 he received testosterone propionate, 25 mg intramuscularly 3 times weekly because of soreness of the left breast, this caused no change in the size of the breasts but the soreness was perhaps improved. There was never any secretion.

He first noticed pubic hair at 14 and began to have nocturnal emissions the same year. Intercourse was always satisfactory. The voice remained high pitched until he took thyroid at 26 at which time the voice became deeper, he could still voluntarily pitch his voice high, and was occasionally mistaken for a girl over the telephone. He

started to shave at 21, and now shaves every day. Recession of the hair above the temples was first noticed at 21 and has slowly progressed (see fig 1, D).

For 5 years he has had mild nocturnal characterizations by uncontrollable attacks of sleeping and cataplexy. Four years ago, he had left renal colic when a small stone lodged at the uretero-vesical junction. He was admitted to the hospital and finally passed the stone. On analysis it contained phosphates and oxalates. He had always been a heavy milk drinker. Serum calcium was 11.5 mg per cent, serum phosphorus was 3.2 mg per cent. During the next 4 years, he had a few mild attacks of colicky pain on the left side, during which he passed small stones.

Examination showed a tall, well developed swarthy male. The span was not significantly greater than the height. Axillary, pubic and perineal hair were normal. Beard and body hair were heavy. There was marked recession of the hair above the temples. The voice was somewhat high pitched but definitely masculine and the larynx was normal in size. The breasts were greatly enlarged, the nipples were enlarged and pigmented. The left breast was slightly tender, without masses and the left nipple was retracted somewhat. No secretion could be expressed. The phallus, scrotum and prostate were well developed. The testes were quite small, measuring about 2.0 cm in length. They were firm, normally sensitive and about equal in size. The epididymides were well developed.

Hinton test was negative. Roentgenograms showed a normal sella turcica, normal bone age, and normal kidney outlines without evidence of stones. Intravenous pyelogram showed normal urinary passages. BMR was -12. The urine was of high specific gravity (1.028) and contained large amounts of calcium. Many oxalate crystals, a few leukocytes but no albumin. Cultures showed a light growth of *staph. albus*. Serum calcium was 10.3 mg per cent, serum phosphorus was 2.8 mg per cent. Semen examination showed azoospermia. Biopsy of both testes showed complete hyalinization of the seminiferous tubules and normal appearing interstitial cells (fig 4, A). Biopsy of the left epididymis revealed entirely normal tissue.

Bilateral subcutaneous mastectomy was performed in July, 1942, the breast tissue showed ductal hyperplasia and proliferation of the periductal connective tissue (fig 6 B).

Case 7, SC (private patient of Dr H. I. Suby), a 32-year-old married Jewish school teacher, complained of sterility. He had been married for 4.5 years. He had mumps at 10 without orchitis, and had never had any trauma to the testes. At 27 he had a urethral discharge which cleared promptly with methenamine treatment, there were no complications with this infection and no recurrences. He was always obese. Puberty began at 13 and progressed normally, intercourse was satisfactory, and he had ejaculations. Hair and beard growth were normal. At 16 he first noticed prominence of the breasts, which have increased in size very little since that time.

Examination showed an obese, well developed male with normal axillary, pubic and facial hair. The span was not significantly greater than the height. The voice was low pitched. The breasts were moderately enlarged, not tender and no secretion was expressed. T

scrotum, and prostate were fairly well developed and within normal limits. The testes were small.

Semen examinations repeatedly showed azoöpermia. Biopsies of the right testicle showed impaired spermatogenesis with hyalinization of the seminiferous tubules and normal appearing interstitial cells. The patient was treated with chorionic gonadotropin, 750 to 1,000 U intramuscularly 3 times weekly for 3 months without any change in the size of the testis or breasts and without improvement in the appearance of the testis biopsy (fig. 4, B). He continued to have azoöpermia. He was then treated with testosterone propionate, 25 mg. intramuscularly 3 times weekly with no noticeable effect.

*Case 8* (fig. 1, E), C.G. (M.G.H. 12047), a 35-year-old married Jewish porter, was admitted at the age of 31 complaining of sterility and gynecomastia. His general health was always good. He had mumps at 8 without orchitis; he had never suffered any injury to the testes and said they were 'always small.' At 19 an appendectomy was performed; it was noted then that the testes were small and the breasts were enlarged. Puberty began at 14 and progressed normally. At 16 he noticed enlargement of the breasts which progressed for about 3 years and has since remained stationary (fig. 3, B); the breasts were never painful or tender and no secretion was present. He married at 25 and had satisfactory intercourse with ejaculations but no pregnancies resulted. He had slowly gained weight during the last 10 years.

Examination showed an obese, well developed man with smooth skin. There were telangiectases of the cheeks. Axillary, pubic and perianal hair were normal; head hair was heavy and there was a slight recession of the hair above the temples. There was a myopia and a few lenticular opacities; the visual fields were normal. The voice was deep and the larynx was of normal size. The breasts were greatly enlarged and resembled those of an adolescent female; they were not tender and no secretion was expressed. The phallus, scrotum, and prostate were well developed. Both testes were very small.

The FSH was positive for at least 10 M.U. per 100 cc. of urine. Estrin assay was negative for 10 R.U. per liter of urine. The glucose tolerance test was not remarkable. Roentgenograms showed a normal sella turcica, a normal right adrenal after perirenal air injection, and union of the epiphyses of the radius and ulna. Basal metabolic determinations were -20 and -26. Serum cholesterol was 138 mg. per cent. Semen examination showed azoöpermia. Biopsy of the left testis showed almost complete hyalinization of the seminiferous tubules and normal interstitial cells. Biopsy of the right breast showed hyperplasia of the ductal epithelium and proliferation of the periductal connective tissue.

The patient was seen in 1942 with the same complaints. He married again at 32 and his second wife had not become pregnant. The breasts were not changed. During the last year, libido had decreased but he still had erections, intercourse and ejaculations. He shaved only once a week and the beard was limited to the chin and upper lip. It is interesting that his father who had 11 children had the same type of beard.

Examination revealed essentially the same findings as

before. The span was not significantly greater than the height. The epididymes as well as the phallus, scrotum and prostate were well developed. The testes were very small, about 1.5 cm. in length, and equal in size. Hinton test was negative.

*Case 9* (fig. 1, F), A.C. (M.G.H. 249898), a 38-year-old married Jewish merchant, was admitted in May, 1940, complaining of sterility. He had married 3.5 years before and his wife had not conceived although no contraceptives were used. After pneumonia at the age of 6 he had infrequent hemoptyses.

Examination revealed bilateral gynecomastia, very small testes and signs of cavitation in the right upper lobe. Roentgenograms showed chronic cystic disease of the right lung; the sella turcica was normal. The visual fields were normal. Semen examination revealed azoöpermia.

In 1942 he was seen again, still complaining of sterility. There was no history of mumps or orchitis. The testes were 'always small.' Puberty began at 12 and progressed normally. He had satisfactory intercourse with ejaculations. He shaved twice a week. Breast enlargement was first noted at 18 when he was thin. During the next few years he slowly gained weight and the breasts increased in size. The breasts were never painful or tender and had not changed in size for the last 10 years (fig. 3, C).

Examination showed a well developed muscular man. The span was 4.5 cm. greater than the height. Axillary, pubic and perianal hair were abundant; head hair was heavy and there was recession of the hair line above the temples. The beard was limited to the chin and upper lip, but was quite heavy. The voice was deep and the larynx normal in size. The breasts were greatly enlarged, but not tender and no secretion was expressed. There were signs of cavitation over the right upper lobe. The phallus, scrotum, and prostate were normal. The testes were extremely small, equal in size and firm. Hinton test was negative. The patient refused to have a testicular biopsy performed.

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# Clinical Evaluation of Estrone, Estradiol Benzoate and Diethylstilbestrol

[Menopause]

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DURING the past several years a large number of articles have been published concerning the scientific and, oft times, speculative aspects of therapy with various estrogenic hormones. Physicians concerned with practical clinical results, and cost per treatment, will find few data in the literature on the relative effectiveness, duration of action, tolerability and cost of the various types of estrogenic substances. However, the physician in his daily practice is interested in how he can attain the best results with the least possible risk of side-effects, and at a cost within the means of his patient. With this in mind, we instituted a survey of a group of more than 200 patients over a considerable period of time.

## MATERIAL AND PROCEDURE

The series under investigation consisted of women in the menopause. The group of patients represented many races, colors and nationalities. In our clinics at Metropolitan and Flower-Fifth Avenue hospitals the patients treated were from among the poorer classes. They included Porto Ricans of Spanish and mixed descent, Italians, Negroes, Jews and a smattering of other nationalities and races. The patients in our private practice, located in a suburb of New York City, were white and financially were of the better class. Thus it will be seen that a fair cross section of New York's polyglot population was surveyed and peculiarities incident to certain groups were eliminated.

The cases ranged from mild menopausal types to those with more severe symptoms of the surgical menopause. However, the majority of cases represented patients with similar symptoms and of not too severe a nature. The patients were divided into 4 groups of 50 each. Those in group 1 received preparations of estrone,<sup>1</sup> which is a product of partial

metabolic inactivation of estradiol; those in group 2, received  $\alpha$ -estradiol benzoate,<sup>2</sup> the synthetically derived benzoic ester of the primary follicular hormone; group 3 received diethylstilbestrol,<sup>3</sup> the new synthetic estrogen which, in contra-distinction to the other two compounds, does not occur naturally in the body; group 4 were treated with ovarian extracts, sedatives and a male hormone preparation.

At the initiation of the investigation, therapeutic effects were measured by estimations of urinary estrin and examination of endometrial biopsies and vaginal smears. Later these procedures were discontinued because of difficulties encountered in correlating some laboratory findings with the subjective response experienced by patients. Therefore, clinical results became the sole criterion for evaluation.

The commonly used parenteral dosage for estrone and estradiol benzoate is 10,000 I.U. (1 mg.) of the former and 2000 R.U. (0.33 mg.) of the latter. These are the arbitrary dosage levels employed in most instances in the respective groups.

Most of the patients in groups 1 and 2 were checked as a 'control' and by giving injections of sterile water it was possible to determine whether psychic factors were responsible for the improvement experienced by the individual. Within 4 to 14 days after initiation of the sterile water injections, all of the women complained of the original ailments. Resumption of hormone treatment brought about such remarkable improvement that there can be no doubt as to the efficacy of the therapy.

Diethylstilbestrol, when injected, was given to most of the patients in doses of 1 mg. Many of those in group 3, receiving diethylstilbestrol, as well as some represented in groups 1 and 2, were given diethylstilbestrol orally in daily doses of 1.0, 0.5 and 0.1 mg., respectively. The total number of patients

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<sup>1</sup> The estrone employed was supplied by E. R. Squibb and Son, New Brunswick, N. J. (Amniotin); Parke, Davis & Co., Detroit, Mich., (Theelin); and Endo Products, New York City (Estromone).

<sup>2</sup> The  $\alpha$ -estradiol benzoate (Dimenformon Benzoate), was supplied by Roche-Organon, Inc., Nutley, N. J.

<sup>3</sup> The diethylstilbestrol (Metestrol) was supplied by Metropolitan Laboratories, New York City.

thus changed to oral therapy with diethylstilbestrol approximated the number present in each original group. Also, as the study progressed, in some of the cases receiving estrone, therapy was changed to estradiol benzoate and vice versa, likewise, patients received diethylstilbestrol injections, supplemented with diethylstilbestrol orally, after their response to estradiol benzoate or to estrone had been evaluated. The reverse sequence was employed in other instances, in which patients were first treated with diethylstilbestrol, orally or parenterally, and therapy was changed to either estrone or estradiol benzoate. Many patients were rotated to all the groups, eventually being returned to estradiol benzoate therapy.

**Dosages and side effects.** There were 2 women in each of the three original groups of patients treated with estrogens, who developed sore buttocks characterized by a rash and swelling at the site of injection. When therapy was changed so that each of these patients received a different estrogenic substance, similar reactions recurred. When given placebo of oil, these patients likewise showed identical by effects indicating the allergy was toward the oil and not the estrogens.

In the group receiving estrone, it was found that, in the average case, the dose of 10,000 I U was sufficient to control the menopausal symptoms for from 4 to 6 days. There were a few instances in which relief could be obtained only when two injections per week were given, and a smaller number in which partial relief only was obtained even though injections were given as frequently as three times a week.

The group of patients receiving  $\alpha$  estradiol benzoate experienced the most prolonged beneficial effects. Most of the patients, on a dose of 2000 R U, were kept symptom free for 8 to 10 days, although a few required more frequent injections while a number were able to go as long as 2 to 3 weeks between injections. Aside from the local reactions previously noted, which definitely were not attributable to the therapy, no untoward side effects were observed in the groups receiving the estrone or  $\alpha$  estradiol benzoate.

Group 3, receiving diethylstilbestrol, is of special interest because of the comparatively recent introduction of the medication. It was found that if injections of 1 mg. were given, the interval between injections and recurrence of symptoms was very short. By increasing the dose to 2, and even 5 mg., the period between injection and recurrence of symptoms was not markedly increased, but the toxic phenomena were manifested more promptly, and were more severe. By effects included nausea and vomiting, skin rash and soreness or fullness of the breasts. Two patients complained of insomnia and disturbing dreams when they did fall asleep. The symptoms disap-

peared when the dosage was reduced or after rest periods of about a week.

Diethylstilbestrol is the only estrogen therapy used in the study where an oral administration to a large number of patients was attempted, and here the greatest percentage of toxic manifestations was observed. With a daily dose of 1 mg., there was nausea and vomiting in 4 cases, 8 per cent. Nausea alone was noted in 7 additional cases, or a total with gastrointestinal phenomenon of 22 per cent. When the dosage was cut to 0.5 mg. daily, the incidence of gastrointestinal symptoms decreased to 6 per cent, and on a dosage of 0.1 mg. twice daily, only one patient, or 2 per cent of the series, reported nausea. Unfortunately, when the dosage was so decreased, the effectiveness was so lowered that it became a question whether the side effects of the diethylstilbestrol were less objectionable than were the occasional hot flushes, vertigo and similar menopausal manifestations.

The results observed with ovarian extracts are definitely inferior to those attending the use of either estradiol benzoate or estrone. In some instances sedatives gave relief from such symptoms as emotional instability or excitability, other manifestations, however, such as flushes or vertigo did not abate on sedation alone. Testosterone propionate proved definitely beneficial, but its use was, in our hands, limited to cases with a tendency to uterine hemorrhages.

#### CASE REPORTS

The following case histories illustrate the procedure employed to evaluate the various substances and also the results attending therapy.

**Case 1 S.D.**, white, age 43, para 2. Except for influenza in 1918 and cystitis in 1939, there had been no serious illnesses and no operations. The menstrual history was a normal one. When she was first seen in October 1940, the patient complained of pain in the precordial region, vertigo and hot flushes. Physical examination, including an electrocardiogram, revealed no cardiac pathology. The Wassermann reaction was negative. Therapy with estrone, 10,000 I U parenterally, twice a week for 6 injections was followed by marked symptomatic improvement. Injections of the hormone were then replaced by injection of sterile water without the patient's knowledge, after 2 weeks the symptoms became as severe as at the beginning of treatment or more so. Therapy with 2000 R U of estradiol benzoate parenterally, once a week, was instituted in January, 1941. Complete symptomatic relief followed the 4th injection. A vaginal smear, made on February 4, showed little cornification, round or oval atrophic cells being prevalent, notwithstanding subsidence of clinical symptoms. In March, therapy was shifted to diethylstilbestrol orally, 0.5 mg., twice a day. There was slight nausea and pruritus of the thorax and genital region. The pruritus subsided after about 6 days. Subsequent recurrence of daily hot flushes and vertigo under this regimen necessitated a return to therapy with es-

tradiol benzoate parenterally. Under the latter the patient again became symptom-free, remaining so to date (June, 1942) on a maintenance dose of 2000 R.U. every other week.

*Case 2. M M.*, a white female of Spanish descent was 31 years old. There had been a unilateral oophorectomy performed in August, 1935. Following this the intervals between menses, which preoperatively had occurred regularly every 28 to 31 days, increased to 2 to 3 months. When first seen, Feb. 1, 1940, the patient complained of amenorrhea (last period October, 1939), severe attacks of hot flushes, vertigo, nervousness and pain in the precordial region. The face and upper extremities showed a wide-spread acne vulgaris which occurred after cessation of menstruation. An electrocardiogram was negative, although the chest plate showed slight enlargement of left ventricle and slight accentuation of the arcs of the pulmonary artery and left auricle. Therapy with estrone, 10,000 I.U. parenterally, twice a week was instituted. On Feb. 29, 1940, the patient reported improvement. Bleeding occurred on March 2 and 23 at which time she was symptom-free. A reduction of the dosage to one injection of 10,000 I.U. of estrone weekly was followed by return of symptoms, June 18. From then on 2000 R.U. of estradiol benzoate was given once a week instead of the estrone. This dose sufficed to relieve completely all symptoms. Medication was continued until Sept. 10, 1940, the patient experiencing a sense of well-being at all times. Injections of hormone were then replaced by injections of sterile water and 1 mg. of diethylstilbestrol per day orally was given simultaneously. By November, 1940, severe headache, hot flushes, marked vertigo, fatigue and sluggishness were manifested. On November 1, injection of 1 mg. of diethylstilbestrol, twice a week, was substituted for the oral therapy. The flushes and vertigo were relieved to some extent, but the symptoms did not clear up completely. In February, 1941, therapy was changed again to estradiol benzoate, parenterally, 2000 R.U., once a week. Complete symptomatic relief followed the fifth dose. The patient remained symptom-free except for an occasional slight flush on a maintenance dosage of 2000 R.U. every other week, which dosage was instituted on March 15, 1941. Headache, present when diethylstilbestrol was administered, did not recur after discontinuance of therapy with the substance or when other estrogens were given.

*Case 3. A.A.*, age 37, gravida 1, nullipara. Menarche occurred at 15 years of age, with menstrual cycles 25 days in length, menstruation lasting 3 to 4 days. When the patient was first seen in February, 1940, she complained of irregularity in the menses for the previous 6 months. The bleeding periods recurred at intervals of 50 to 65 days with a scanty flow. Hot flushes, vertigo, and extreme nervousness were also experienced. The symptoms cleared up promptly with estradiol benzoate, 2000 R.U. parenterally once a week. Menses became more frequent but there was no change in the amount or duration of flow. In April, injections were discontinued and diethylstilbestrol, 1 mg. orally were given daily. The occurrence of severe nausea and vomiting prompted reduction of the dosage to 0.5 mg. of diethylstilbestrol daily.

On this smaller dose there was recurrence of flushes and complete anorexia. In May, 1940, oral medication with diethylstilbestrol was discontinued, being replaced with estradiol benzoate parenterally, 2000 R.U., once a week. On July 9, 1940, the patient was symptom-free and was discharged. Observations at intervals of 3 months showed no recurrences of symptoms (March, 1942).

*Case 4. S.L.*, age 57, nullipara. Menarche at 13 with cycles of 28 to 30 days and a menstrual flow lasting 5 to 6 days with occasional slight pain. Menses ceased at the age of 53 and the patient had infrequent hot flushes and spells of vertigo for which she did not seek medical attention. In September, 1938, she presented herself for examination because of spotting every few days for the previous 6 weeks. Upon manual examination a small nodule on the anterior aspect of the uterus was found. Curettage revealed the presence of carcinoma and a pan-hysterectomy was performed immediately following the diagnosis. The pathologist's report indicated a carcinoma adenomatousum. The convalescence following operation was uneventful. The patient returned in January, 1939, complaining of a typical anginal syndrome. An electrocardiogram revealed an inversion of the T-wave and depression of the S-T segment. Associated with this change were frequent hot flushes, vertigo, nervousness and insomnia. Physical examination revealed an apex rate of 96 per minute with a well-defined diastolic murmur at the apex. There were no evidences of carcinoma at the site of operation or in any other part of the body. Estradiol benzoate parenterally, 2000 R.U., twice a week, for 5 doses, was followed by complete relief of symptoms. After the 12th injection a second electrocardiogram revealed a normal pattern. The patient has been seen once a month up until June, 1942, and several electrocardiograms made subsequently have been negative. With improvement in cardiac symptoms, the hot flushes and other menopausal symptoms have disappeared as well.

*Case 5. N.V.*, age 38, para 3, gravida 3. Menarche occurred at 12, with cycles 28 to 30 days in length, and menstrual flow for 4 to 6 days, pain preceding the onset and lasting for first day. Following childbirth, the patient experienced occasional dysmenorrhea. In July, 1940, a pan-hysterectomy had been performed because of uterine fibroids and cystic ovaries. When the patient was first seen in October, 1940, she complained of severe dizzy spells, headache (both frontal and occipital) and hot flushes. Diethylstilbestrol, parenterally, 1 mg. was given twice a week. A vaginal smear, made after 6 weeks under this regimen, showed epithelial cornification but there was no abatement of symptoms. Injections were supplemented by 1 mg. of diethylstilbestrol, orally, per day. This resulted in only slight improvement. After 12 weeks of treatment with diethylstilbestrol, therapy was changed to estradiol benzoate, 2000 R.U. parenterally, twice a week. The clinical response was prompt and the patient became symptom-free after 3 weeks. Subsequently, the dosage was reduced to 2000 R.U. of estradiol benzoate once a week, on which dosage the patient remained symptom-free for more than 3 months. In May, 1941, therapy with estradiol benzoate was discontinued and diethylstilbestrol, 1 mg. orally was administered once daily. After 2

weeks, the symptoms returned and the patient requested to be given the parenteral treatment. Estradiol benzoate, 2000 R U, every other week was given and continued until December, 1941, when the patient was discharged. Re-examination in February and May, 1942, showed the patient to be comfortable and without symptoms except for an occasional slight hot flush.

### Cost of Treatment

The following table illustrates the efficiency of the three estrogens, estrone, estradiol benzoate, and diethylstilbestrol, in comparison with the cost of treatment.

| Drug Used   | Average Duration of Effect | Toxic Reaction | Average Cost to Patient per Unit of Treatment <sup>1</sup> | Average Adjusted Monthly Cost |
|---|----------------------------|----------------|--|-------------------------------|
| Estrone, 10,000 R U = 1 mg (parenterally)               | days<br>4-6                |                | \$1.10   | \$6.60                        |
| α Estradiol benzoate, 2000 R U = 0.33 mg (parenterally) | 8-10                       |                | \$0.65   | \$2.16                        |
| Diethylstilbestrol, 1 mg (parenterally)                 | 2-3                        |                | \$0.16   | \$2.00                        |
| Diethylstilbestrol tablets, 1 mg (orally)               | 1                          | 22%            | \$0.0135   | \$0.41                        |

<sup>1</sup> Prices based on those charged in representative drug stores in midtown and suburban New York. Figures for diethylstilbestrol are based on average prices charged for a low priced brand.

### DISCUSSION

From the foregoing data, it is obvious that diethylstilbestrol has the benefit of being low in cost. However, the reactions and toxic by-effects observed in this study call for caution and a careful test to determine individual sensitivity to the drug before prescribing it.

Most interesting is the observation that those patients originally treated with estradiol benzoate, if treatment was changed to estrone, had to be given more frequent injections than those who were treated initially with estrone. Those whose treatment started with estradiol benzoate had experienced the sense of well being that may be attained with comparatively small doses of this compound. Subsequently, more frequent injections, or, in terms of units per month, higher doses of estrone were required to alleviate symptoms adequately than was the case with those patients who originally were treated with estrone and who had never experienced the maximum sense of well being attending the use of estradiol benzoate. Conversely, if therapy of patients with estrone were changed to estradiol benzoate, not only were less frequent injections necessary, but the patients also experienced a greater sense of well being.

Furthermore, it was observed that patients who initially received estradiol benzoate, particularly cases of surgical menopause, when therapy was changed to diethylstilbestrol, required both parenteral and oral doses of the latter compound to main-

tain comfort. In the present series, diethylstilbestrol was effective in the doses administered in only 30 per cent of the cases, in which the patients initially had received estradiol benzoate.

In a recent report, Stoddard and Metzger (1) discussed comparative effectiveness and costs of estrogenic therapy and reached conclusions which differ somewhat from our own. These differences, it would seem, are the result of using different methods of evaluation. Stoddard and Metzger employed the technic commonly used in determining estrogenic effects in animal experimentation, whereas we observed that complete cornification of the vaginal

cells may occur without relationship to relief of symptoms, and hence vaginal smears may not always be a reliable index to therapeutic response. For this reason we discontinued making vaginal smears shortly after the study was instituted, and thereafter relied solely on clinical response as an index to potencies, dosages and cost of treatment.

It is also observed that Stoddard and Metzger base their findings on studies of women of the post-menopausal period (55 to 70 years of age) who, without exception, were mental patients. In our series, aside from a few pre-menopausal cases, patients were at the beginning of the menopause, natural as well as surgical, and none was a mental case. It is also to be noted that evidently endocrine balance had been already fully established in the group studied by Stoddard and Metzger, which was the reverse of our series. This difference in the type of patient, particularly as regards mental status and age, naturally has a bearing on the observations and is perhaps the basis on which vaginal smears were chosen by Stoddard and Metzger as the method of measuring response.

The fact that the cases in the group studied by Stoddard and Metzger represented patients who apparently were not in the distress because of climacteric symptoms and whose mental status made their testimony unreliable, no doubt accounts for the 10 day period of observation as defined by the authors. In our series, all of the patients presented symptoms requiring treatment over an extended period of time. Results were judged solely by the degree of comfort

experienced by the patient during the period of endocrine adjustment. We are inclined to believe that caution should be exercised in comparing the results observed by Stoddard and Metzger with those reported herein. In the one study, the methods of bioassay commonly employed in animal experimentation served as an index of therapeutic effectiveness, whereas in the other, (our own) clinical methods alone were used. As an instance, in the clinic one observes the slow absorption of estradiol benzoate which makes spacing of doses possible, while such a response in an animal under observation for a week or 10 days and receiving daily injections cannot be accurately measured.

#### SUMMARY AND CONCLUSIONS

A series of more than 200 menopausal women, in four groups of equal size, was subjected to treatment with estrone, parenterally, estradiol benzoate, parenterally and with diethylstilbestrol, some of which was given orally, some parenterally; the fourth group

received ovarian extracts, sedatives and a male hormone preparation. By rotating patients to various groups of treatment it was attempted to evaluate therapeutic potencies and the cost of treatment.

Side-effects such as gastro-intestinal phenomena were observed in 22 per cent of the group receiving diethylstilbestrol. While the cost of this estrogen, not native to the body, is low, the toxic reactions it elicits call for caution in its use. Estrone and estradiol benzoate were well tolerated. When symptoms require more constant supervision, and by-effects are to be avoided, or if there is lack of co-operation on the part of the patient, parenteral is preferable to oral therapy. Results observed in the present study lead to the conclusion that the  $\alpha$ -estradiol benzoate is the estrogen of choice. Injections can be spaced conveniently because of the protracted action of the esterified compound and its cost is far lower than that of estrone.

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# Oral Hormone Therapy in Anovulatory Bleeding

## [Ovarian Failure]

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COMBINED EFFORTS in various fields of investigation have contributed to the understanding of the physiologic background of menstruation. In a slow but steadily progressive course, theories of the earliest writers have yielded to more concrete knowledge as developed from the application of anatomic, physiologic and biochemical facts. These facts were augmented by biologic experimentation built around the physiology of the female generative apparatus and centered in the theory of the dominating rôle of the corpus luteum in the mechanism of menstruation.

Contradictory to this construction, is the observation of the non ovulatory menstruation. The work of Corner (1) and Hartman (2) proved that anovulatory bleeding occurs in the Macacus rhesus occasionally and at times other than during the summer months. Novak (3) in 1930 transferred these facts to the realm of human physiology, assuming that certain types of irregular bleeding, although of a cyclic character, likewise occur without the activity of the corpus luteum.

The following case, observed in the Endocrine Clinic of the Woman's Hospital, was studied over a comparatively long period. It is presented as a contribution to the problem of alutal bleeding and as evidence that such a condition can be influenced by therapeutic methods.

### CASE REPORT

Mrs. M.C., 32 years old, was seen first Sept. 7, 1940. Complaints: For the last 2 years, severe pounding head aches at frequent, irregular intervals, increasing before menstruation, fatigue and the feeling of fullness. The menstrual cycle, which was regular up to two years before admission, is now of a 35 to 45 day type and the flow is gradually decreasing in amount.

The patient is of feminine configuration, moderately obese, 5 ft. 3 in. tall, and weighs 172 lb., she has lost 20 lb. during the last 3 years. The B.M.R. was minus 8%. Pelvic examination revealed a somewhat enlarged uterus in normal position and normal adnexa.

On Sept. 21, 1940 an endometrial biopsy (premenstrual phase expected) showed a proliferative phase of the endometrium with numerical decrease of glands. A diagnosis of edema of proliferative endometrium was made (fig. 1). The patient was given diethylstilbestrol, 1 mg. daily, which was tolerated without side effects. On Oct. 5, 1940 bleeding occurred, lasting 5 days. This was considered by the patient, to be the first normal menstruation in several years.

An endometrial biopsy on Nov. 2, 1940 was diagnosed as hyperproliferation of endometrium of mild degree (fig. 2). Bleeding occurred Nov. 3 to 8, 1940. This was considered by the patient to be identical with normal menstruation, since in the preceding curettage, November 2, a luteal phase could not be detected, this bleeding was considered to be of the alutal type.

Treatment with diethylstilbestrol was discontinued and she was given pregnenolone, 60 mg. daily for 7 days preceding the next expected period. Bleeding occurred on Dec. 1, 1940 the character of which had not been determined by an endometrial biopsy prior to onset of flow. During the second half of the following cycle, 80 mg. of pregnenolone was given daily for 2 weeks. An endometrial biopsy made Dec. 28, 1940, was diagnosed as a non-secretory endometrium in a moderately hyperproliferative state, the hypertrophic process was less pronounced than in the previous curettage (fig. 3). Bleeding for 7 days of moderate extent began on Jan. 1, 1941.

On Feb. 3, 1941 the patient was given pregnenolone, 60 mg. daily for 5 days, followed by 100 mg. daily for 7 days, a total of 1000 mg. being given. An endometrial biopsy made on Feb. 15, 1941 was diagnosed as a fully developed secretory phase (fig. 4). Menstruation began on Feb. 17 and continued until Feb. 22, 1941.

During the second half of the following cycle, the patient was given 1000 mg. of pregnenolone. On the first day of menstruation March 15, 1941, an endometrial biopsy again revealed a full secretory phase (fig. 5).

During the next period the patient received no therapy. An endometrial biopsy made on April 11, 1941 was diagnosed as a well built premenstrual endometrium, two days prior to onset of menses after a four weeks' pause in medication (fig. 6).

Subsequently the patient was given small doses of desiccated thyroid extract, no other hormone therapy being given. In April, May, August, and October of 1941 endometrial biopsies were done close to the expected

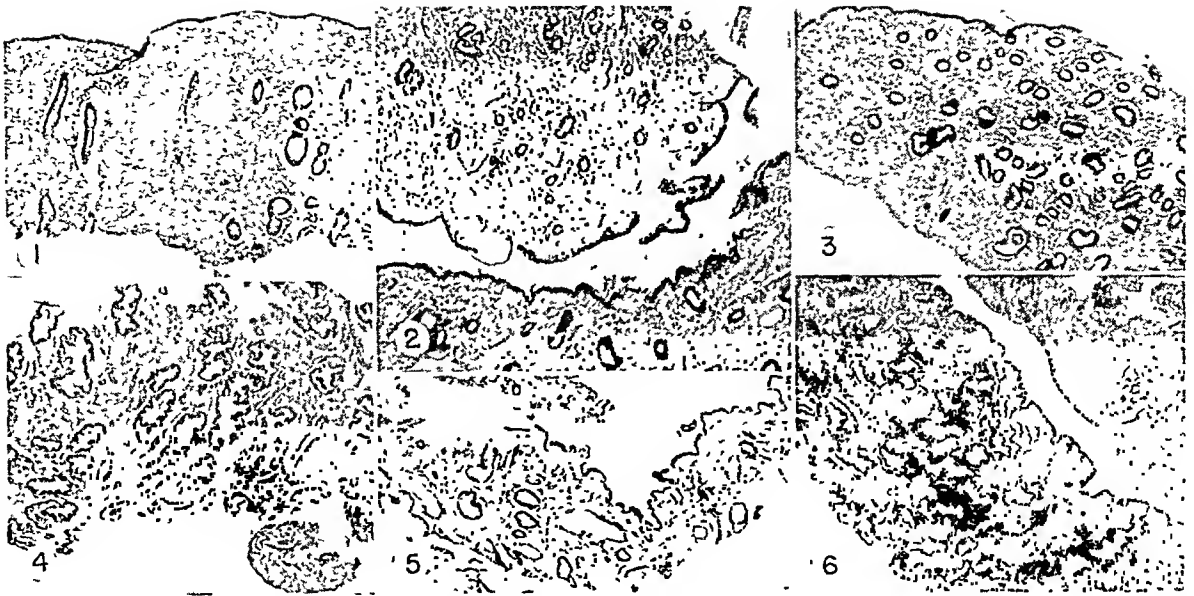


Fig. 1. BIOPSY OBTAINED Sept. 21 1940. Proliferative endometrium.

Fig. 2. BIOPSY OBTAINED Nov. 2, 1940 following therapy with 1 mg. of diethylstilbestrol daily since Sept. 21, 1940. Previous menstruation Oct. 5-9. Hyperproliferation of mild degree. Menstruation followed on Nov. 3 and lasted 6 days.

Fig. 3. BIOPSY OBTAINED Dec. 28, 1940 after 2 weeks of treatment with 80 mg. of pregnenolone daily. Non-secretory endometrium, moderate proliferation. Menstruation followed on Jan. 1 and lasted 7 days.

Fig. 4. BIOPSY OBTAINED on February 15, 1941 after receiving a total of 1000 mg. of pregnenolone in the 12 days preceding the biopsy. Secretory endometrium. Menstruation followed on Feb. 17 and lasted until Feb. 22, 1941.

Fig. 5. BIOPSY OBTAINED Mar. 15, 1941 on first day of menstruation. Patient had received 1000 mg. of pregnenolone during second half of cycle. Secretory endometrium.

Fig. 6. BIOPSY OBTAINED Apr. 11, 1941, two days before onset of menses. No treatment had been given during this cycle. Secretory endometrium.

onset of menstruation; all revealed a secretory endometrium, normal for the premenstrual phase. Menstruation occurred at regular intervals of 28 days and were of normal character. Coinciding with the return of the normal type of uterine bleeding, the physical condition of the patient improved and she reported she was well when last seen.

In analyzing this case it may be emphasized that experimental investigations seem to indicate that menstruation is essentially composed of two phenomena, a), the dissolution of the structure of the endometrium initiated by a sharp drop in the level of the ovarian hormones, which is coinciding with a liberation of the pituitary hormone; b) the bleeding mechanism proper. The postulate that the corpus luteum is the dominating factor responsible for menstruation, as it follows from the work of Fraenkel (4), was irreconcilable with newer viewpoints evolved from the recognition of the anovulatory cyclic bleeding in the monkey and in the human female from a non-secretory mucosa. This fact *per se* lends support to the concept that the bleeding mechanism is independent of the corpus luteum and is in all probability essentially a vascular phenomenon. The corpus luteum, therefore, is the responsible factor for the transformation of the proliferative endometrium into a secretory mucosa and for the maintenance of secretion. The fact that cyclic uterine bleeding, menstrual or intermenstrual, is preceded

by a sudden drop in the level of the female sex hormone, lends support to the assumption that the female sex hormone plays an essential rôle in cyclic uterine bleeding.

Experimental neurology has brought to light the importance of the hypothalamus as the center of a neuro-glandular mechanism, which also controls, among other vegetative functions, some activities of the generative apparatus (5). Hohlweg and Junkmann (6) have shown by their experiments that the sex hormones do not act directly upon the hypophysis by way of the blood stream, and conclude that an interpolated sex center, presumably represented by the hypothalamus, acts as a regulator between these two organs. The vascular phenomenon in menstruation, therefore, may result from the vasomotor stimulation of the uterus (endometrium) generated by the neuro-glandular interaction and, therefore, is temporally linked with the gonad activity. Subsequently the cyclic uterine bleeding may be maintained by the sex center also under conditions in which the hormone constellation necessary for normal menstruation is disturbed, such as in anovulatory menstruation, when the corpus luteum hormone is not produced.

With reference to the effectiveness of the substitutional hormone supply in the case presented, one may be well justified in assuming restoration of the entire physiological mechanism of the menstrual cycle

by supporting all tissues involved in their intrinsic readiness to respond. By administration of those hormones produced in the sequence of a complex physiological process, such as menstruation, one may promote recuperation and thereby readjustment of normal function, which when unaided, may be greatly delayed or not resumed at all.

The first three endometrial biopsies, which preceded the first three bleeding episodes under observation, combined with the physical symptoms, may give suggestive evidence that the patient was in a state of disturbed hormonal balance. Restoration of normal function became manifest only after the hormone

supply was increased to the required optimum, which was affected by oral administration.

The pregnenolone (Progesterone) was supplied by Roche Organon Inc., Nutley, N. J. by the courtesy of Dr. Leo A. Pirk.

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# Treatment of Acne with Orally Administered Estrogens<sup>1</sup>

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IN A PREVIOUS paper (1) we proposed the thesis that acne is caused by a disturbance of the normal balance between androgens and estrogens. When the imbalance becomes such that there is a preponderance of the androgens the acneogenic action of the androgens which Hamilton (2) has demonstrated, is exerted.

In support of this thesis we reported (1) the results of assays of androgens and estrogens in 33 female patients with acne. The results of the assays indicated significant androgen preponderance as compared to normal standards. No assay of urine from males was reported, for we were unable to obtain dependable estrone equivalent values from males.

If this thesis concerning the cause of acne is correct, it should be possible to bring about the disappearance of the eruption by administering sufficient estrogen to restore the androgen-estrogen balance to normal, and males as well as females should respond to the treatment. The present communication concerns the results of such treatment in 25 individuals, 14 females and 11 males.

## SUBJECTS

The histories and physical findings in the group yield certain data which demand brief discussion. The well-known association of acne with adolescence, and its tendency to spontaneous remission toward the end of that period, make the age factor extremely important in interpreting our results. In this series only 3 females and 4 males were under 20 years of age. The average age of the 14 women was 25.8 years, that of the 11 males, 20 years. It seems unlikely therefore, that spontaneous remission can be an important source of error in evaluating therapy in this series.

The duration and severity of the process must also be considered in interpreting results, since the tendency

to spontaneous remission of mild and recent eruptions is common. In 5 of the patients the duration of the acne was between 1 and 5 years; in 12, between 5 and 12 years; in 4, between 12 and 20 years; and in the remaining 3, between 20 and 30 years. The average duration for the group was 9.1 years. The process was graded as a), moderately severe, 12 patients; b), severe, 10 patients; and c), extremely severe, 3 patients. No patient was included in the series who had had, during the preceding year, any marked improvement in the condition. Nineteen had had previous treatment with roentgen-ray, ultraviolet light, or 'sun lamps,' without benefit. Possible error due to spontaneous remission would, therefore, be minimal.

In the group of 14 female patients there was none whose menstrual history was normal. Seven complained of severe dysmenorrhea, 8 of hypomenorrhea, and 2 of menorrhagia. In 13 there were definite exacerbations of the acne at the time of menstruation, followed by variable improvement, never amounting to complete disappearance, during the intermenstrual intervals.

## TREATMENT

The patients were treated either with diethyl stilbestrol or with ethinyl estradiol<sup>2</sup> by mouth. Twenty received diethyl stilbestrol; five, ethinyl estradiol. The initial dose of the former was 0.5 mg. daily until tolerance was determined. In 17 patients it was then increased to 1 mg. daily, and in two mature males with severe chronic acne to 1.5 mg. and 2.0 mg. daily. In women the medication was omitted 4 days before the predicted menstrual period, and resumed 48 hours after menstruation had ceased. Therapy was uninterrupted in males. In only one patient was it necessary to stop the diethyl stilbestrol because of persistent digestive disturbance. When ethinyl estradiol, 0.15 mg. daily, was used there was no disturbance. None of the males experienced any digestive disturbance. In two males slight gynecomastia, and in one,

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<sup>2</sup> The ethinyl estradiol was supplied by the Schering Corp., Bloomfield, N. J., through the courtesy of Dr. Erwin Schwenk and Dr. Max Gilbert.

pigmentation of the nipples, appeared, but receded rapidly when treatment was omitted in the two who have remained under observation. This reaction suggests that it may be wise to employ intermittent treatment in males as well as in females.

Ethinyl estradiol was administered in initial doses of 0.15 mg daily. This was later increased to 0.3 mg, if the response was unsatisfactory. No unpleasant reactions were observed, and it appeared to be as effective as stilbestrol.

#### RESULTS

Fifteen of 25 patients (60% of the series) became entirely free from acne after periods of treatment varying from 2 to 6 months. Two patients, whose treatment was intermittent, became free in 8 and 9 months, respectively. The 8 remaining patients are still under treatment, and all show improvement, varying between 50 per cent, in a woman of 36 with acne and hirsutism of 21 years' duration, and 90 per cent, in 4 months, in a boy of 13 with severe generalized acne of the face, neck, chest and back. No patient has completely failed to respond. All of the female patients, with the exception of the one with hirsutism, have shown a synchronous improvement in menstrual difficulties of a degree comparable to the response of the acne.

#### DISCUSSION

The high incidence of abnormal menstruation in our series cannot be explained on the theory of chance, and furnishes a basis for believing that acne is associated with an imbalance of hormones, the nature of which is suggested by the characteristic cyclic variation in the severity of the eruption. During catamenia, the estrogens are low, while the androgens do not fluctuate significantly (3-6). There is, therefore, a relative estrogen deficiency at the time of exacerbation of the acne at menstruation, and the eruption improves, or even disappears in the mild cases, as the estrogens increase to their mid cycle peak. Geist and his associates (7) have shown that the injection of testosterone in women brought about 'regressive changes in the endometrium and vaginal smears characteristic of estrogen deficiency,' and that, coincidentally, mild acne appeared in a number of patients, and disappeared as endometrium and vaginal mucosa regenerated rapidly following the cessation of the testosterone injections.

If their conclusions and our deductions are valid, it should be possible to cause the disappearance of acne in an individual by producing, by means of therapy, a constant increase in the estrogens in the body of sufficient magnitude to restore the normal dynamic estrogen androgen balance.

Our initial experiments with gonadotropic and

estrogenic therapy furnished intriguing, but unsatisfactory, results (8, 9). In some adolescents with mild acne, complete and apparently permanent disappearance of the acne followed treatment with urinary gonadotropic extracts, but in the older patients with more severe acne good results were partial and the benefit temporary. These suggestive, but unconvincing, results may have been due to failure of ovarian response to the dosage used, as seems especially likely in the adults, or to the fact that it was impossible in most cases to give the injections as often and as long as necessary. Similar results were obtained with injections of estrogens, all of which suggested that the unsatisfactory response might be due to insufficient or ineffective therapy.

The response to estrogen therapy in the present series of patients furnishes, we believe, evidence concerning the cause of acne. As an isolated study our series is too small to afford conclusive proof, but if the results are correlated with biological and experimental data, they become significant. A brief recapitulation of these data is, therefore, pertinent.

The most significant of these biological facts are: a) that acne does not occur spontaneously in male castrates, and is extremely rare in the first decade of life, a time when both androgens and estrogens are present in only minimal amounts (10), b) acne is characteristically associated with adolescence, during which time both estrogens and androgens are normally increasing rapidly (in amount), and c) acne usually disappears spontaneously in early adult life when the normal dynamic balance between estrogens and androgens has become established. As a corollary, the high incidence of abnormal menstrual cycles in adult female patients with acne indicates that failure to establish such a normal balance, or its interruption (by a masculinizing tumor, for example), is a common factor in both the acne and the abnormal menstrual cycle.

The exact nature of this disturbance cannot be determined from this biological evidence, although the close association of acne and masculinizing tumors, and the high androgen titers, suggests that an excess of 17 ketosteroids is the determining factor in acneogenesis. This suggestion is supported and clarified by Hamilton's observation that injections of testosterone will produce acne in many, but not all, male castrates, (2) and by the observation of Geist and his associates (7) that some, but not all, of their female patients treated with testosterone developed temporary acne during treatment. The only possible interpretation of these results is that the so called 'male hormone' is acneogenic, but that it can produce acne only in individuals who are not normally resistant to its acneogenic potentialities.

The factors which determine this resistance are, as

emphasized in our previous paper (1) probably multiple, but as was also pointed out, both biological evidence and hormone assays suggest that the controlling factor is a disturbance of the balance between androgens and estrogens, resulting in insufficient estrogenic potency to protect the individual from the acneogenic effect of androgens. The biological evidence consists in the well-known menstrual exacerbation and inter-menstrual remission of acne in certain women. The levels of androgens have been shown to remain fairly constant throughout the menstrual cycle (3, 4), while the estrogens show a cyclic variation, reaching their lowest level at the time of menstruation and their highest level at about the middle of the cycle. The association of the exacerbation of acne with catamenia, and the remission during mid-cycle, therefore, furnish further evidence of this anti-acneogenic property.

The results of adequate estrogenic therapy in patients of both sexes, as reported in this paper, furnish, we believe, further evidence that acne is caused by a disturbance of the normal functional balance between androgens and estrogens, and that when the preponderance of the androgens becomes sufficient in an individual, that it exerts a specific acneogenic effect. If this be true, the diagnostic significance of acne, and the method of treating it successfully, are also established.

#### SUMMARY AND CONCLUSIONS

Twenty-five patients (14 females and 11 males)

with acne, were treated with diethyl stilbestrol or ethinyl estradiol. Fifteen patients (60%) became entirely free from acne in from 2 to 6 months. Two more, in whom treatment was intermittent, became free in 8 and 9 months. The 8 remaining patients are still under treatment, and all show improvement. No patient has completely failed to respond. The biological and recent experimental evidence concerning the cause of acne is reviewed and it is concluded that such evidence, together with the results of adequate estrogen therapy, furnish evidence that acne is caused by a disturbance of the normal functional balance between androgens and estrogens when the preponderance of the androgenic factor becomes sufficient to exert its specific acneogenic effect in a given individual.

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# Dosage of Female Sex Hormones, Estradiol and Anhydrohydroxyprogesterone by Sublingual Application

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SOME TIME ago I reported in this journal on favorable results which had been obtained by the sublingual administration of methyl testosterone (1). Good results had been observed with the female sex hormone, estradiol, by this form of application, both in animal experiments (2) and clinically (3-6). It has been deemed desirable to determine the dosage of female hormone necessary to produce the proliferative and secretory phase in the human endometrium by sublingual application, particularly in view of the fact that no such reports are today available. It is known that dosages as high as 450 mg of estradiol administered per os are not sufficient to produce endometrial proliferation in a castrated woman (3), according to Herrenberger this can be done with 180 mg of estradiol in alcoholic solution by sublingual administration. Giesen (5) succeeded in producing proliferation of the uterine mucosa with dosages of 150 to 180 mg of estradiol, in the form of tablets which he allowed to dissolve in the mouth. In animal experiments Miescher and Gasche (2) showed that the action of estradiol on the uterus of the castrated female rat is 10 to 20 times more intense sublingually than orally.

On the basis of these observations, 6 women between 48 and 55 years of age who had had roentgen therapy 2 to 3 years previously because of recurring metropathy and who subsequently suffered from severe ovarian deficiency symptoms were chosen for the following experiments. They were given tablets of estradiol and of anhydrohydroxyprogesterone especially prepared for sublingual administration.<sup>1</sup> These hormones are mixed with mucilaginous drugs and emulsifying agents which promote absorption and are then compressed at high pressure. The patients placed the tablets under the tongue or in the pouch of one cheek where the tablet slowly dissolved. In contrast to the usual peroral method of enteral administration, we shall designate this as 'sublingual' in order to avoid confusion.

## CASE REPORTS

*Case 1* K. S., 50 years old; gravida 2, para 2, menarche at 12 years of age. Menstrual periods occurred every 4 weeks, lasting 4 to 5 days, and were of average intensity. For some months there had been metrorrhagia, an endometrial biopsy showing glandular hyperplasia. Repeated roentgen treatment had been given (each time about 90 r) which stopped the hemorrhage. Patient complained of tiredness, outbreaks of sweating, and itching of the external genitals. From April 14th to 28th, 1942, the patient received daily 6 tablets sublingually, each containing 1 mg of estradiol, a total of 60 mg. Endometrial biopsy on April 28th showed proliferation of the mucosa. The patient then received from May 1st to 3rd and from the 9th to 12th, 5 mg of anhydrohydroxyprogesterone in tablet form sublingually, a total of 150 mg. Biopsy of the endometrium on the 28th day of the cycle showed a transformation toward a secretory phase with glycogen deposits. On May 13th menstruation started which lasted for 5 days. Since then the patient has remained free from complaints.

*Case 2* W. F., 55 years old, gravida 12, para 7, menarche at 16. Menstrual periods occurred every 3 weeks lasting 6 to 7 days, very profuse. A curettage was performed in 1939 because of menometrorrhagia which had persisted for a year. The histological diagnosis was a glandular cystic hyperplasia of the endometrium. In consideration of the patient's age, a single treatment with roentgen ray (approx 230 r per ovary) was given. There has been no hemorrhage since July, 1939. During the last few months the patient complained of hot flushes and insomnia.

From April 17th to May 1st, 1942, the patient has taken daily 5 tablets sublingually each containing 1 mg of estradiol, i.e. a total dose of 75 mg within a period of 15 days. The endometrial biopsy on May 2nd showed that the uterine mucosa was in the proliferative phase. From May 6th to 11th, 1942, the patient received 5 tablets sublingually of anhydrohydroxyprogesterone, i.e. 150 mg within 6 days. The patient began to menstruate on the 26th day of the cycle (May 12th). The endometrial biopsy made on the same day showed some secretory transformation with glycogenic deposits in the glands, menstrual disintegration of the mucous membrane was the predominant characteristic. Menstruation lasted from May 12th to 16th, was of medium intensity and stopped spontaneously. Hot flushes and insomnia disappeared.

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<sup>1</sup>The preparations of estradiol and of anhydrohydroxyprogesterone were supplied by the Society of Chemical Industry, Ciba, Basle, Switzerland.

*Case 3. W. R.*, 52 years of age; para 2; menarche at 16. Menstrual periods had occurred every 4 weeks lasting 4 to 5 days, and were fairly profuse. Curettage was performed in 1939 because of metrorrhagia. Glandular hyperplasia (histologically confirmed) recurred soon afterwards. The patient received roentgen-ray treatment with approximately 230 r per ovary. This patient also complained of mild ovarian deficiency symptoms.

The patient received 4 tablets of estradiol sublingually daily from April 18th to May 2nd, 1942, i.e. a total of 60 mg. An endometrial biopsy made on May 4th showed a proliferative endometrium. From May 6th to May 11th 5 tablets sublingually per day of anhydrohydroxyprogesterone were administered. On May 13th, the 26th day of the cycle, bleeding occurred. A biopsy made on the same day showed the endometrium in a state of menstrual disintegration. The bleeding stopped after 4 days, on May 16th. The patient stated that she 'felt better.'

*Case 4. B. S.*, 48 years of age; menarche at 14. The menstrual periods recurred every four weeks, lasting 9 days, and were fairly profuse. There had been two abortions and no normal birth. Meno-metrorrhagia had persisted for 6 months. Endometrial biopsy showed glandular hyperplasia of the endometrium. The patient then received a single roentgen-ray treatment, approximately 240 r per ovary. Soon afterwards mild headache, hot flushes and temporary pruritus occurred.

From April 18th to May 2nd, 1942, the patient received daily 4 tablets of estradiol sublingually, i.e. a total of 60 mg. within 15 days. Biopsy made on May 5th showed a proliferative endometrium. From May 6th to May 11th, the patient received sublingually 5 tablets of anhydrohydroxyprogesterone, i.e. a total of 150 mg. within 6 days. On May 12th, the 25th day of the cycle, bleeding started, lasting for 3 days, and then ceased spontaneously. This patient was particularly benefited by the treatment, as all previous complaints such as headache, hot flushes and itching disappeared.

*Case 5. W. B.*, 48 years old; para 2; menarche at 15. Menstrual periods recurred every 3 to 4 weeks lasting for 8 days, and were very profuse. At 17 there had been juvenile bleedings. Since 1938 she had had meno-metrorrhagia. This had increased in severity during the last few months of 1939. The patient was curetted in December, 1939, and the diagnosis was that of glandular cystic hyperplasia. She then was given a single treatment of 240 r per ovary. No hemorrhages have occurred since, but there have been headaches, outbreaks of sweating and debility.

The patient received sublingually, daily, from April 19th to May 3rd, 1942, 5 tablets of estradiol, i.e. 75 mg. within 15 days. Endometrial biopsy on May 4th showed that the endometrium was in the proliferative stage. From May 9th to May 14th, 1942, the patient was given sublingually daily 5 tablets containing 5 mg. anhydrohydroxyprogesterone, i.e. 150 mg. within 6 days. The endometrial biopsy made on May 15th (the 27th day of the cycle) showed a fully developed secretory phase with glycogen deposits in the glands. Bleeding continued subsequently until May 20th when menstruation ceased. The patient stated that she felt better after treatment.

*Case 6. S. W.*, 51 years of age; menarche at 13. Menstruation occurred every 4 weeks, and was profuse, lasting 5 to 6 days. There had been 6 normal pregnancies. For the last year the patient had had irregular, profuse menstruation. Endometrial biopsy in 1939 showed glandular cystic hyperplasia. After a single roentgen-ray treatment of approximately 230 r per ovary, the hemorrhages ceased. The patient still suffered, however, from hot flushes, headache and articular pain.

From April 20th to May 4th, 1942, the patient received sublingually 4 tablets of estradiol daily, i.e. 60 mg. within 15 days. Endometrial biopsy on May 5th showed the proliferative phase. From May 11th to May 16th she received daily 25 mg. of anhydrohydroxyprogesterone sublingually in the form of tablets i.e., a total of 150 mg. Menstruation, lasting for 3 days started on May 17th. The patient's complaints were relieved.

*Endometrial biopsies* following treatment with doses of 60, 75 or 90 mg. of estradiol in the form of tablets prepared for use sublingually, show the proliferative phase in endometrium of the human female after roentgen therapy. This fact seems to be all the more important as Reifferscheid and Schmidt (4) required, in the case of a female castrate, 300 to 400 mg. of a glucoside compound of estradiol by ordinary peroral administration to induce the proliferative phase in the endometrium, but only 150 to 195 mg. of estradiol in alcoholic solution on sublingual administration. Herrenberger (3) also reports transformation of the endometrium in a female castrate after the sublingual administration of 180 mg. of estradiol in alcoholic solution. We obtained the same effect with estradiol in the form of specially prepared tablets for sublingual administration with one-half to one-third of the dosage employed by the above workers (fig. 1).

The ratio between the sublingually active dose of estradiol and the injection dose of estradiol dipropionate is between 2 and 3:1 as we have always produced endometrial proliferation in a female castrate by the injection of 25 to 30 mg. of estradiol dipropionate.

Further, a transformation of the endometrium of a female castrate toward the secretory phase has been obtained with 150 mg. of anhydrohydroxyprogesterone in the form of tablets, especially prepared for sublingual administration.

In a previous paper (7), we were able to show that the secretory phase in the endometrium with subsequent menstruation, after previous proliferation, could be effected by the peroral administration of 220 to 300 mg. of anhydrohydroxyprogesterone in women who had received roentgen-ray therapy some years before. This was 5 to 8 times as high as the dose of progesterone required by injection. By sublingual administration, the same effect can be obtained with about 3.5 times the injected dose (fig. 2).

With reference to the mechanism of the hormone action after sublingual application, the advantage of

this method of medication is based on the particularly favorable conditions of absorption from the oral mucous membrane, whether it is via the blood stream (8) or via the lymph passages (9). Following the ingenious investigations of Pedersen Bjerregaard (10) it has been shown that 90 per cent of estrone absorbed through the portal vein is inactivated by the liver.

The explanation for the discrepancy between the dosage of estradiol which has been found effective in these investigations and those of Herrenberger, Reiferscheid and Schmidt is probably to be found in the different method of preparation and administration of the same hormonal substance. Whereas the latter workers employed alcoholic solutions, we used the tablets especially prepared for sublingual administra-

after 3 to 6 months of treatment. Two of the patients unfortunately failed to return after beginning treatment. In one patient no menstrual period has yet occurred in spite of two series of treatments. The patients who were successfully treated received sublingually doses of 30, 44 and 75 mg of estradiol, respectively, in the form of tablets. This amount of hormone produced proliferation of the endometrium. Subsequently, doses of 75, 100 and 150 mg of anhydrohydroxyprogesterone sublingually in the form of tablets produced the progestational effect with menstrual bleeding.

#### CASE REPORT

*Patient T. E.*, was a 35-year old female with acromegaly who had had amenorrhea for 4 months, and prior to that



Fig. 1 Tissue obtained by endometrial biopsy of a patient treated with 60 mg of estradiol sublingually in the form of tablets showing the endometrium in the proliferative phase.

Fig. 2 Tissue obtained by endometrial biopsy of a patient treated, after estradiol priming with 150 mg of anhydrohydroxyprogesterone sublingually in the form of tablets showing the endometrium in the early secretory phase.

tion, as already mentioned. These contain the hormone in the form of an aromatic melted mass, compressed into tablets under heavy pressure, they slowly dissolve in the saliva and are uniformly absorbed. The superiority of these tablets as regards absorption is seen from the detailed experiments of Wattenwyl (11) to which we would particularly refer.

After the dosage of estradiol and anhydrohydroxyprogesterone had been determined in patients with castration symptoms who had had roentgen therapy, a number of patients with other gynecologic disorders were treated. Detailed clinical reports of these cases are being published elsewhere and only a few examples are briefly mentioned here. These cases are cited to show not so much the success of treatment as the efficacy of the sublingual method of application of the female sex hormones.

Nine cases of secondary amenorrhea of 3 to 15 months' duration were treated, the age range was 17 to 27 years. In 6 cases, menstruation was effected

time oligomenorrhea. Roentgenograms showed an enlargement of the sella turcica. There was amblyopia in the left eye. Considerable enlargement of the extremities had occurred. The basal metabolism had increased +32%. A moderate amount and normal distribution of pubic hair were present, the vagina was narrow but smooth. Portio was of normal height, the collum anteverted. The uterus was antelected, smaller than normal, firm, easily movable, adnexa free. The endometrial biopsy showed an atrophic mucosa.

*Treatment.* A total of 75 mg of estradiol was administered sublingually in the form of tablets over a period of 15 days. Biopsy showed proliferation of the endometrium. Bleeding started 48 to 72 hours after discontinuation of treatment, lasted for 13 hours and ceased following three intramuscular injections of 1 mg of estradiol dipropionate. A full course of treatment was then given sublingually using 60 mg of estradiol and 150 mg of anhydrohydroxyprogesterone, both in the form of tablets. Menstrual bleeding occurred from the 26th to the 28th day of the treatment cycle. The patient stated that she no longer suffered from the troublesome headaches after the menstruation.

A second cycle of treatment sublingually with 75 mg. of estradiol in 9 days and 25 mg. of anhydrohydroxyprogesterone daily for 6 days, a total of 150 mg. was followed by bleeding on the 21st day lasting 5 days. A third course of treatment with anhydrohydroxyprogesterone alone was begun 12 days after menstruation had ceased. After a total of 75 mg. in 5 days bleeding occurred which lasted 4 days.

Up until the present time there has been relief from headache, although the objective state is unchanged.

A further series of 18 cases with various indications for therapy, such as glandular hyperplasia of the endometrium, threatened abortion, hypoplasia with oligomenorrhea, dysmenorrhea and climacteric deficiency symptoms were treated alternating the two sex hormones which were administered sublingually. The impression was gained that this much simpler and more pleasant method of administration of the hormones is not inferior in action to treatment by injection. Because of the particularly favorable conditions for sublingual absorption this may become the method of choice for treatment in the future.

#### SUMMARY

Six women who had received roentgen-ray treatment of the ovaries in 1939, were treated with 60, 75

or 90 mg. of estradiol sublingually. Proliferation of the endometrium was produced. By subsequent sublingual administration of 150 mg. of anhydrohydroxyprogesterone secretory changes in the endometrium were obtained. The characteristics of proliferation and secretion were verified by endometrial biopsy and histological examination.

The mode of sublingual application of the female sex hormones is briefly discussed and a few clinical examples given.

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# A Case of Delayed Induction of Menstruation in Primary Amenorrhea

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A 23 YEAR OLD white woman, married for 2 years, was referred in March, 1935, for sterility. The patient had never menstruated. She had married at 21 years of age. Still having complete amenorrhea 6 months later she consulted a physician who prescribed theelin and chorionic gonadotropin. This was taken for 3 months without results.

The mother had not menstruated until she married, then only at irregular intervals, and there had been only one pregnancy. The patient's personal history was not remarkable. She stated that she felt well except for frontal headaches which occurred frequently when she was excited or tired. She fatigued easily.

Physical examination revealed an attractive young woman of boyish figure whose height was 64.8 in and weight 117.7 lbs. There was only slight mammary development. The pubic hair had a tendency towards masculine distribution. The axillary hair was abundant, and there was a sufficient excess of facial hair that treatment for its removal at regular intervals by electrolysis was required. Skiagrams of the skull showed nothing abnormal. Vaginal examination revealed a small uterus, and the ovaries could not be felt on bimanual examination.

The laboratory findings (blood and urine) were within the normal range. There was a daily excretion of 25 M.U. of estrogen and 7 to 8 mg. of 17 ketosteroids as measured by the photoelectric colorimeter. Repeated basal metabolic rate determinations gave values from 60 to 90 per cent of normal, averaging about 80 per cent. Blood pressure readings taken at the same time were as follows: 108/72, 98/60, 100/62, 112/82 mm Hg.

Anthropomorphic measurements were: bust 30.3 in, waist 25.3 in, hips 35.2 in, height to symphysis 33.3 in, height 64.7 in, span 63.8 in.

The patient was given thyroid therapy<sup>1</sup> starting at 1 grain and gradually increasing to 3 grains daily. She was also given 1 cc. of anterior pituitary extract<sup>2</sup> daily

and 1 cc. of theelin<sup>3</sup> every other day for two weeks periods during the next year. No noteworthy change occurred except that she lost the tired feeling, the breasts increased slightly and the hips markedly in size. The measurements were: bust 25.3 in, waist 30.7 in and hips 37.6 in. There was also some growth of the uterus but the ovaries were still not palpable.

On Sept. 11, 1936, she was given pregnant mare serum<sup>4</sup> intramuscularly, 5 units daily, in the thighs. One week later this was increased to 10 units. This dosage caused an intense local reaction with redness and swelling, and the inguinal glands became swollen and tender. The dosage was reduced again to 5 units daily, alternating the legs as the site of the injection. After two weeks the swelling which occurred with each injection ceased and did not recur. One month later, in October, each ovary was barely palpable. On November 30 both ovaries were enlarged and tender. Measurements at this time showed: bust 26.0 in, bust 31.5 in and hips 38.2 in. The dosage of pregnant mare serum was increased to 10 units daily for two weeks and then a rest period of two weeks was interposed. On December 14 both ovaries were found to be enlarged, easily palpable and tender. The following month each was the size of a large walnut and very tender. The dosage was decreased to 5 units daily. This treatment was continued with injections at two week intervals until October, 1937, when therapy was discontinued, the ovaries then being the size of a plum and still very tender. It was believed that the ovaries had become cystic and that further medication was inadvisable. The following April, 1938, a final checkup showed that the ovaries had decreased in size and were no longer tender.

<sup>2</sup> The anterior pituitary extract was that of E. R. Squibb & Sons, New Brunswick, N. J.

<sup>3</sup> The estrogen (Theelin) was manufactured by Parke, Davis & Co., Detroit, Mich.

<sup>4</sup> The pregnant mare serum (Gonadogen) was supplied by the Upjohn Company, Kalamazoo, Mich.

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<sup>1</sup> The desiccated thyroid was supplied by Armour & Co., Chicago, Ill.



Nothing further was heard from the patient until Sept. 24, 1939, when she first menstruated, having a normal period lasting 5 days. There was a second period from November 2 to 7 after a 39-day interval. A third period of flowing occurred from November 18 to 24 and the periods were regular during December, 1939, and January and February, 1940.

In February, 1941, she reported that she had not menstruated since the preceding February. An examination at this time showed that there had been a decrease in the bust measurement to 30.9 in. and in the hip measurement to 37.2 in. The facial hair was somewhat more prominent. The ovaries were no longer palpable. The basal metabolic rate was 75 per cent of normal. Treatment with pregnant-mare serum was resumed at 10 units three times weekly, after a preliminary test for sensitivity. After the first two injections the inguinal glands became swollen and tender, but there was no inflammation at the site of the injection. This condition subsided after the omission of one injection and did not recur. Thyroid was again given, 2 grains daily. After 4 months of treatment at 2-week intervals the bust measurement had increased to 33.0 in. and the ovaries had become enlarged and slightly tender. Treatment was continued until December, 1941. During January, 1942, there was a slight flowing lasting 2 days. At this time the injection of pregnant-mare serum was followed by two weeks' treatment with 1 mg. of progesterone every other day for 8 doses. No period occurred in February or March,

and all medication except thyroid was discontinued on March 16, 1942. A regular menstrual period lasting 5 days began on April 20, 1942.

Vaginal smears made twice weekly during the past year showed a regular increase in estrogenic action during each period of medication. No endometrial studies were made.

The following is offered as a possible explanation of the long delay in the appearance of the menstrual periods which began two years after medication was stopped. The action of the pregnant-mare serum caused an increase in follicle maturation but the follicles failed to rupture. This resulted in a condition of cystic ovaries. After cessation of medication the cysts slowly regressed until a balance was reached between waves of follicle maturation and regression; at this point menstruation occurred. The recurrence of menstrual periods after a second course of treatment lends weight to the assumption that menstruation was the result of the effect of the medication on the ovaries.

#### SUMMARY

The case is reported of an amenorrheic young woman who gave no immediate response to treatment with pregnant-mare serum but who began to menstruate for the first time two years after cessation of the treatment. After another amenorrheic period of a year, menstruation again occurred following treatment with the serum and desiccated thyroid as adjuvant.



# Observations on the Mechanism of Uterine Bleeding

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**A**N INTELLIGENT therapeutic approach to the problem of menometrorrhagia will result only when the mechanism of uterine bleeding is fully understood. The artificial induction of pseudo-menstrual bleeding in the castrated human female clarifies many controversial points. The data on the case to be reported has been charted in figure 1.

## CASE REPORT

ZMD, a white female, 28 years of age, presented herself at the Endocrine clinic of the University Hospital during the latter part of 1939 complaining of severe menopausal symptoms. One year previously she had been submitted to laparotomy and both fallopian tubes and ovaries were removed because of tubo-ovarian abscesses. From Nov 14 to 16, 1939, a 48 hour urine specimen was obtained and the urine was found to contain an insufficient amount of estrogen for assay. The vaginal smear revealed a castrate or 1+ reaction. A curettage was performed on Nov 16, 1939 and no endometrium could be obtained. From December 7 to 22 the patient was given 1 mg daily of diethylstilbestrol<sup>1</sup> orally, during which time she noted that the breasts had become full, libido had increased, the hot flashes were ameliorated and the vaginal smears revealed a 3+ reaction. Beginning on December 18 she received 10 mg of progesterone<sup>2</sup> parenterally per day for 4 days. Uterine bleeding began on December 26, and a thorough curettage was made one hour after onset. No tissue could be obtained. The curette felt gritty on scraping it against the wall of the uterine cavity. Bleeding lasted 3 days. One mg daily of diethylstilbestrol orally was again administered from Dec 29, 1939 to Jan 22, 1940. Beginning on January 19 she received 10 mg of progesterone daily for 3 days. A suction curettage was performed on January 24 and no endometrium was obtained. Bleeding started 2 days later and lasted 5 days. During February, 1940, she had two short courses of diethylstilbestrol (fig 1) and in March, 1940, she received along with the diethylstilbestrol therapy 8 injections of 10 mg each of progesterone. Following cessation of therapy the patient was hospitalized to await the onset of bleeding. This occurred 2 or 3 days later and within a few hours of its onset a thorough dilatation and curettage was performed under anesthesia. Histologic sections of the ma-

terial obtained on this occasion, as on other occasions, revealed only blood clot, fibrin, some endocervical mucous glands and/or cervical epithelium but no endometrium.

Bleeding episodes were induced on several other occasions following estrogen-progesterone therapy. Progesterone alone proved ineffective, for progesterone withdrawal

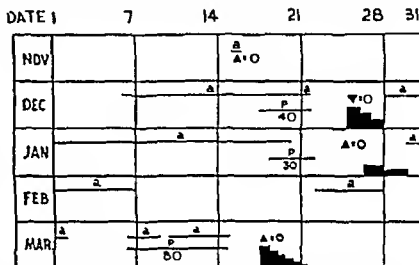


FIG 1 INDUCTION OF UTERINE BLEEDING IN A CASTRATED FEMALE. Triangle, dilatation and curettage; inverted triangle, suction curettage; O, no endometrium obtained; a, 1 mg of oral diethylstilbestrol per day; p, parenteral progesterone in 10 mg doses.

bleeding could not be induced unless there was priming by estrogens or the simultaneous administration of estrogens and progesterone.

This case study is enlightening for it emphasizes that menstruation is not to be considered as a 'kind of abortion of the embedded unfertilized ovum' as defined by Powers in 1821. This long-accepted tenet has been proven unacceptable since endometrial studies have revealed that anovulatory bleeding is not an uncommon occurrence. The endometrium mirrors ovarian activity and the rôle played by the endometrium is only contributory and not of primary importance. Uterine bleeding may occur from a gestational, a hyperplastic, a persistent estrogenic or an atrophic endometrium. In this case thorough curettage yielded but the minutest amount of scrapings and the tissue obtained was not endometrial but was from the endocervix. The failure to obtain sufficient endometrium within one hour after onset of flow for study on 3 occasions following massive doses of estrogen and progesterone therapy, is sufficient evidence of the minimal rôle

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<sup>1</sup> The diethylstilbestrol was supplied by Eli Lilly and Co., Indianapolis, Ind.

<sup>2</sup> The progesterone (Lutocylin) was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

played by the endometrium in bleeding. Sudden withdrawal of estrogen-progesterone therapy was followed on several occasions by a menstrual flow but bleeding did not occur subsequent to withdrawal of large doses of progesterone (50-80 mg.) alone. These findings substantiate the contention that menstruation is the result of a sudden deprivation of estrogen or of progesterone in the presence of estrogen and that pathologic bleeding is based on the same mechanism of fluctuating levels of ovarian hormones. There is, therefore, no distinction between menstrual bleeding and menometrorrhagia. This case study, on the basis of proven insufficiency of the endometrium further emphasizes and confirms the observations of Bartelmez (1) that the myometrium and its vascular supply are dependent upon endocrine control and are responsible for uterine bleeding. Bartelmez believes that the explanation for the reduction or stoppage of the flow of blood to the mucosa must be sought for in the myometrium and not in the endometrium. The perivascular interlacing arrangement in the uterine muscle makes it easy to understand that the degree of contraction and relaxation of these muscle bundles may have much to do with regulating the duration and amount of menstrual bleeding. Excessive uterine

bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict or be constricted, following the initial extravasation of blood distally. Menstruation is fundamentally a vascular phenomenon in which the endocrines play the underlying rôle.

#### CONCLUSIONS

1. With estrogen-progesterone therapy uterine bleeding could be induced at will in a young female, surgically castrated one year previously. When progesterone alone was administered, bleeding did not follow.
2. Failure to obtain endometrium on thorough curettage before and after therapy indicated complete atrophy of the endometrial lining.
3. The hormonal induction of bleeding to simulate a menstrual episode on three occasions in this patient would appear to emphasize the importance of the myometrium and its vascular supply and the minimal rôle played by the endometrium in this bleeding.

#### REFERENCE

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# A Case of Schizophrenia in a Hypogonad Man

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THE SCHIZOPHRENIC psychosis presents numerous features suggestive of psychosexual immaturity. Usually, however, the patients are not remarkable for evidences of somatic sexual abnormality. Likewise, attempts to treat the psychosis with androgens have not, in our hands at least, given consistently favorable results. Possibly the failures in the treatment may be due to reduced reactivity to the hormone. Since eunuchs and eunuchoids are not only more responsive to androgens than are normal individuals, it was a matter of interest when opportunity arose to study an individual who was both eunuchoid and schizophrenic—a rare combination.

## CASE REPORT

The patient, H J, was an unmarried, 44 year-old man of Scotch Irish extraction, who entered the Worcester State Hospital on first admission Dec 31, 1941.

The family history was scanty and not relevant to the current problem.

As to personal history, the patient was born by normal delivery after a normal pregnancy. As a little boy he had been 'puny'. He had had severe pneumonia at 2, and the 'usual children's diseases' without known sequelae. In childhood he was regarded as a 'sissy', being much addicted to crying. His school life was undistinguished and he showed little ambition. The voice failed to change at adolescence. He was rejected by the army in 1917 because of what was diagnosed as 'hernia'. The right testis was removed at 34 but the reason could not be determined. It was reported that he became fat following the operation. Some heterosexual interest was claimed and two amorous affairs with women were reported. Most of his recreational time, however, was spent with men and there were suggestions in the history of homosexual attachment.

His industrial history indicated mediocre ability and energy but dependability and stability.

The date of onset of the psychosis could not be precisely determined. In July, 1941, the patient began complaining because he had to work at night and because his helper was very lazy. Little things began to irritate him. His family physician was consulted and advised him to take a temporary rest. Shortly afterwards he began to have

crying spells and complained that the food was of poor quality and that the landlady and his fellow-boarders were irritating. He felt that his fellow workmen were deliberately persecuting him. He was told by his physician that he was going through a masculine equivalent of the menopause.

Upon admission to the hospital in December, 1941, he was found to show stereotyped, odd, manneristic behavior. His emotional reactions were shallow, inappropriate and little influenced by external circumstances. His associations were fragmentary and his speech irrelevant and incoherent with frequent use of neologisms. He was suspicious and somewhat grandiose but rather non-committal in discussing his delusions. His judgment was poor and he was completely lacking in insight regarding his illness. The diagnosis was schizophrenia, 'other types'—i.e., not conforming consistently to any of the Kraepelinian subtypes.

Physical examination revealed that he was tall, well-developed, and slightly over-weight. He was prematurely gray and the body hair was sparse. The escutcheon was of the feminine type, as was the fat distribution. The voice was high-pitched. Slight varicosity of the veins of the legs was recorded. The right testis was absent and the left was notably hypoplastic, as was also the prostate.

Laboratory examinations showed normal blood pressure, pulse rate and rectal temperature. The oxygen consumption rate could not be accurately determined because of poor co operation, but a downward trend suggested that the true basal metabolic rate was probably low. The urine volume was somewhat scanty, the range for 24 hour samples being from 680 to 1580 cc. The creatine output was zero in 3 of 4 collections—a subnormal rate for a schizophrenic. The creatinine output was normal, ranging from 0.913 to 1.211 gm/24 hr. The total nitrogen per 24 hours was definitely low, ranging from 4.63 to 7.35 gm. The 17 ketosteroid output, as determined by the electrocolorimeter, ranged from 5.7 to 7.8 mg/24 hr, which was definitely low as compared with our findings in normal subjects and in most schizophrenics. The blood non-protein nitrogen was 33.3 and the uric acid 2.26 mg/100 cc. The results of the blood study were normal except for an erythrocyte count of 4,410,000. The glucose tolerance was high, a low flat curve being obtained after the ingestion of 100 gm of glucose. He also showed low reactivity to insulin, the drop at one hour being only 16 mg per

cent following intravenous administration of 0.1 u per kg. The blood sugar and blood pressure reactions to adrenalin were both normal.

The diagnostic impression was that the patient was certainly hypogonad. The downward trend of the oxygen consumption rate, the scanty urine, the reduced nitrogen turnover, the secondary anemia, the flat sugar curve and the history of long-standing lack of vigor were thought not to be accounted for, however, by the hypogonadism alone. They were tentatively ascribed to functional hypothyroidism.

Beginning at the end of January, 1942, a therapeutic test was begun with desiccated thyroid,<sup>1</sup> 2 grains daily. At the end of a week the patient had lost 8 pounds of weight and the pulse rate had risen to 90 to 100 per minute. The thyroid was therefore discontinued. The only apparent clinical effect of the material was an increase in excitability. The patient became increasingly elated, frequently pirouetted about the ward for minutes at a time, and often pretended to lead the orchestra while the radio was playing. His speech became increasingly fragmented, practically to the point of 'word salad.'

The attempt at metabolic stimulation was then given up and on February 10, methyl testosterone<sup>2</sup> in dosage of 10 mg. 3 times a week by mouth was begun. A period of 'hypomaniac' behavior with aggressiveness towards attendants and visitors and the necessity for cold-sheet packs ensued. This development was probably in part a carry-over from the previous reaction to thyroid. The methyl testosterone was then discontinued until February 24, following which it was resumed at 10 mg. daily for 2 weeks. The patient was still over-active, requiring sedative hydrotherapy. He then began to improve clinically, and by March 5, was considerably quieter and less active, quite cooperative, friendly and good-humored. He seemed to understand what was said to him but his replies were so complicated by neologisms as to be unintelligible. He had become more careful about his personal appearance. He was detected masturbating.

On March 10 the methyl testosterone was increased to 10 mg. twice daily and on the 23rd, to 3 times daily, with 1 grain of desiccated thyroid added in the hope of increas-

ing the reactivity to the androgen. The patient again became over-active and aggressive, requiring wet-sheet packs, so that on April 6 the thyroid was again discontinued. Ten days later he was quieter and was showing a slight gain in weight. He impressed the psychiatrist as beginning to show considerable homosexual interest in other patients.

Laboratory re-tests during the week of March 21 showed a doubtful increase in the oxygen-consumption rate, slower pulse rate, marked decrease in dextrose tolerance and moderate reduction of insulin tolerance. Other findings, and notably the 17-ketosteroid output, were not significantly altered.

The methyl testosterone was discontinued on April 21. At this time he was showing marked improvement. A week later he was normally quiet and was talking sensibly in a business-like, matter-of-fact way. He had entirely given up the use of neologisms and was working well on a farm crew. He spent much of his time when on the wards in reading.

On May 1 a subcutaneous implant of testosterone was made, 2 pellets of 75 mg. each being inserted. The improved status continued, he being apparently entirely free of the psychosis except for a certain residual amount of underlying suspiciousness and lack of insight. His relatives commented on a remarkable improvement in his personality, stating that he was now as normal as he had ever been.

On May 25 he was dismissed on indefinite visit in care of his family. The closing note comments on his beard's having become slightly heavier and his voice somewhat deeper.

On June 28 the patient returned unaccompanied to the hospital for a re-check. He looked well and was in good spirits. He was planning to resume regular employment in the near future. He was well-composed and rational and showed no apparent signs of psychosis.

#### SUMMARY

The case is reported of a middle-aged eunuchoid who had developed a schizophrenic psychosis. Following the use of methyl testosterone he made a striking recovery from the psychosis and, under the influence of a testosterone implant, at the time of report, had maintained the improvement for two months.

<sup>1</sup> The desiccated thyroid was supplied by the Armour Laboratories, Chicago, Ill.

<sup>2</sup> We are indebted to Dr. Erwin Schwenk of the Schering Corp., Bloomfield, N. J., for the androgen preparations which were used in this case.



# Influence of Methyl Testosterone on Muscular Work and Creatine Metabolism in Normal Young Men<sup>1</sup>

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THERE HAS LONG been a common belief that male sex hormones are associated with muscular strength and endurance. A variety of evidence can be cited in general support of this belief. Increased strength and endurance is one of the most common subjective reports from male castrates and eunuchoids treated with testosterone. Treatment with androgens increased the voluntary activity of castrated male rats (1) and was reported to increase working capacity in adult patients with subnormal or absent testicular hormone production (2). There are numerous reports of the effects of testosterone on nitrogen and creatine metabolism in both eunuchoid and normal men; these suggest a fundamental influence on muscle metabolism and work which has been assumed to be associated with the androgenic activity of the compound. In view of these facts, it is reasonable to inquire whether responses to fatiguing exercise may be altered in normal man by androgen administration. This is a report on the results of experiments on these questions, using methyl testosterone because of its relatively high androgenic effect when given by mouth.

## SUBJECTS

Four healthy male medical students were studied, their ages were between 21 and 30 years. Throughout the experimental period of 11 weeks they maintained their ordinary work in the medical school and subsisted on their usual normal diet except that they ate a meat free meal on the night before each weekly examination.

## PROCEDURE

The experimental period lasted 11 weeks with examination each week. Collection of urine was started

at 6 o'clock on the evening before each examination and was continued until a blood sample was obtained from the subject in the fasting state on the following morning. After this blood sample was taken each man tested his grip strength 5 times with a standard hand dynamometer and the average of the two highest readings was recorded. Each man then ran for 25 minutes at a speed of 7 miles per hour on the motor-driven treadmill set at an angle of 10 per cent climb (vertical climb at 0.7 miles per hour). Blood samples were taken at 8 and at 15 minutes after the cessation of work. Urine collections were made covering the first, second, and third hours from the start of the exercise.

The experimental room was maintained at 78°F, humidity 45 to 55 per cent relative saturation, at all times. All blood samples were drawn from an arm vein, with a minimum of stasis. Blood was received in ice cold tubes, potassium oxalate was used as anticoagulant.

After two weeks for control observations medication was begun. Two men received five 10-mg tablets of methyl testosterone daily while the other 2 men received a like number of placebos made in the same mold. The tablets were taken one after each meal and two on retiring. After 4 weeks the groups were reversed without the subjects' knowledge, the men originally receiving the placebos were now given methyl testosterone and the other pair received placebos. After 3 weeks on this regime the dose was raised to 200 mg of methyl testosterone per day for one week. During the last week of the experiment no medication was given.

It was expected that the methyl testosterone might cause increased creatine storage as had been reported for eunuchoids (3), castrated animals (4), and mature, male rabbits (5) after administration of testosterone. Accordingly, creatine hydrate was administered in capsules containing 250 mg, 4 times a day from the beginning of the fourth week to the beginning of the last week.

<sup>1</sup>Revised manuscript received May 15, 1955.  
Research rendered by the Work Projects Administration, Official Project 165 1271 124, sub projects Nos. 343 and 380. Roche Organon Inc., Nutley, N. J., and Schering Corp., Bloomfield, N. J., generously supplied the methyl testosterone tablets and placebos.

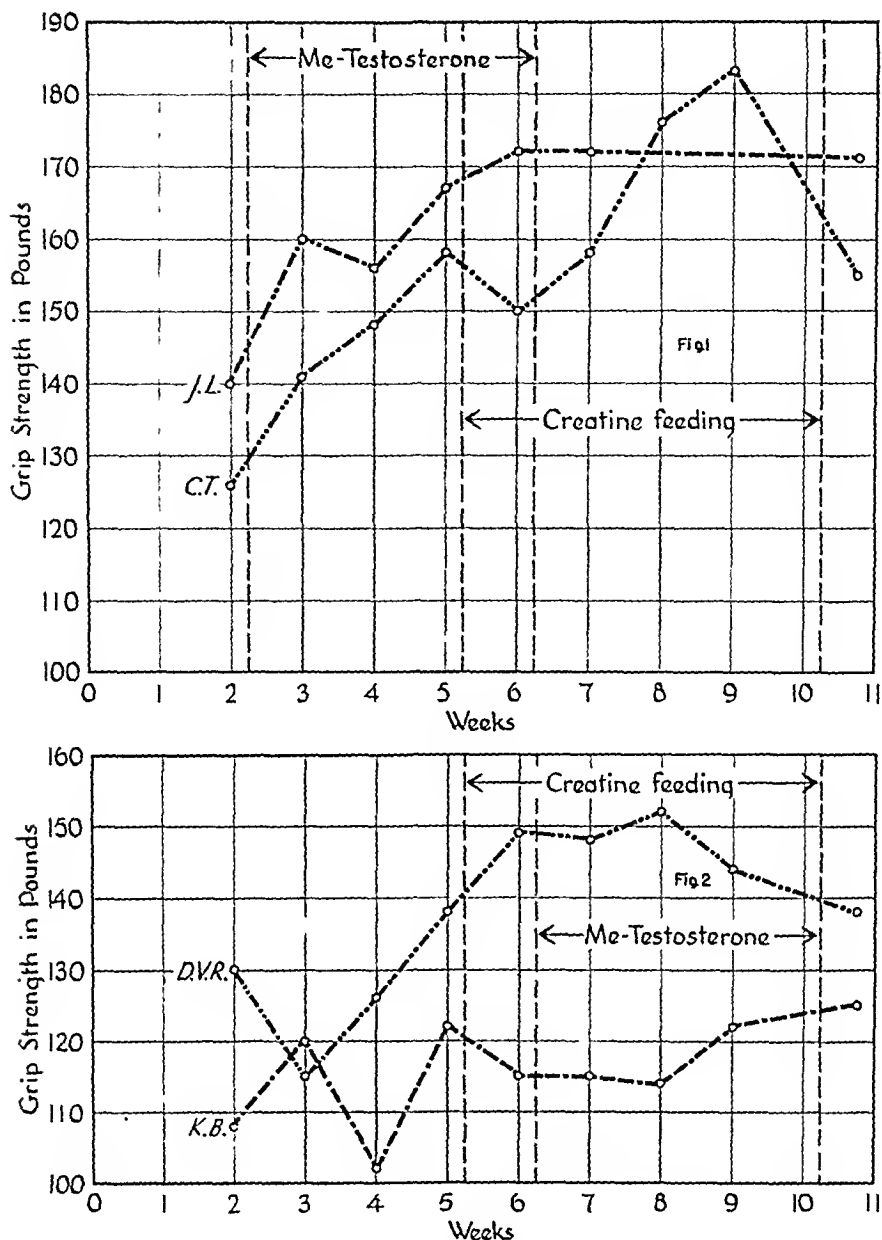


Fig. 1. GRIP DYNAMOMETER TESTS on subjects receiving methyl testosterone during the first part of the experimental period.  
 Fig. 2. GRIP DYNAMOMETER TESTS on subjects receiving methyl testosterone during the latter part of the experimental period.

Basal metabolism was measured on all subjects on the morning of each experimental day in the eighth, ninth and tenth weeks.

#### METHODS

Urine samples were analyzed for total nitrogen, creatine and creatinine. Nitrogen was estimated by the Kjeldahl procedure. Folin's modifications of the Jaffe reaction were used for creatine and creatinine estimations in blood and urine.

Blood lactate was measured by Edward's (6) modification of the method of Friedemann, Cottonio and Shaffer (7). Pyruvate in the blood was estimated by a modification, partly suggested by Dr. E. S. Guzman Barron, of the method of Lu (8). Lactate and

pyruvate in the blood were stabilized with fluoride and iodoacetic acid.

Blood sugar was estimated by the method of Folin (9). Hemoglobin was measured photoelectrically.

#### RESULTS

*Muscular work and ability.* Subjective reports and simple observation disclosed no effects of the hormone administration on physical vigor. Diaries were kept by the subjects. Two of the men recorded a general sense of euphoria which coincided with the period of methyl testosterone administration and one of these men recorded the disappearance of the euphoria when the hormone was withdrawn and placebos were substituted. Aside from a slight train-

ing effect, there was no change in the sense of effort and fatigue in the exercise tests.

The grip-strength tests in 3 men showed a moderate tendency to improve independently of the methyl testosterone administration. The fourth subject showed little change in this score throughout the entire experimental period. Figures 1 and 2 clearly depict the absence of any effect of the medication.

Brief severe work, such as the treadmill test used here, produces characteristic changes in the blood. Perhaps the best quantitative relations to muscular ability and fatigue are seen in the concentrations of lactate and pyruvate, and in the general blood concentration which can be followed by the increase in percentage of hemoglobin. The averages for these variables for two-week periods on each subject are tabulated in table 1. The severity of the work is shown by the magnitude of the changes induced in these variables. There is no significant effect of the administration of methyl testosterone on any of these variables, however, either in the changes from rest or in the indicated rate of recovery after exercise.

Creatine, creatinine and nitrogen metabolism. The concentration of creatinine and non-protein nitrogen in the blood remained very constant throughout the entire experimental period. The creatine concentration, however, showed a distinct tendency to rise during the period of medication in all 4 subjects. In the 2 men who first were given the methyl testosterone and then placebo, there was some tendency for the blood creatine concentration to return toward the

pre-medication level when the drug was withdrawn, but the average values were still above 3 mg. per 100 cc. as long as 4 weeks after the last administration of methyl testosterone. The averages are shown in figures 3 and 4.

The most marked changes were seen in the urinary excretion of creatine, which rose steadily in the period of administration of methyl testosterone and attained levels more than 5 times those of the control periods. Excretions of more than a gram per 24 hours were recorded in a number of instances. Upon change to placebos the urinary output of creatine promptly began to diminish and, in the 2 men who had been receiving placebo for the last 5 weeks of the experiment, the creatine output finally returned to the original control levels during the last week.

These changes in creatine excretion were not accompanied by corresponding changes in the excretion of either creatinine or total nitrogen. Creatinine excretion remained fairly constant. On the whole, total nitrogen excretion tended to diminish throughout the entire experimental period. Since the dietary nitrogen intake was not controlled adequately, it is not possible to ascribe any special significance to the nitrogen output. It is certain, however, that the total nitrogen excretion did not tend to parallel the creatine output. The average values for these urinary excretions are given in figures 5 and 6.

The administration of creatine hydrate during part of the experimental period may be considered to be a complicating factor. It is clear, however, that the

TABLE 1. CONCENTRATIONS OF BLOOD CONSTITUENTS PER 100 CC. EACH VALUE IN THE TABLE IS THE AVERAGE OF MEASUREMENTS FOR 2 WEEKS

| Period, Weeks | Subject | Glucose, mg. |        |         | Hemoglobin, gm. |        |         | Pyruvate, mg. |        |         | Lactate, mg. |        |         |
|---------------|---------|--------------|--------|---------|-----------------|--------|---------|---------------|--------|---------|--------------|--------|---------|
|               |         | Rest         | 8 min. | 15 min. | Rest            | 8 min. | 15 min. | Rest          | 8 min. | 15 min. | Rest         | 8 min. | 15 min. |
| 1-2           | JL      | 96           | 123    | 115     | 14.4            | 15.7   | 15.3    | 1.1           | 3.8    | 4.9     | 9            | 76     | 83      |
| 3-4           | JL      | 87           | 94     | 94      | 14.5            | 15.6   | 15.2    | 1.0           |        | 4.5     | 10           | 96     |         |
| 5-6           | JL      | 96           | 100    | 100     | 14.4            | 15.4   | 14.9    | 1.6           | 4.9    | 4.7     | 11           | 122    | 79      |
| 7-8           | JL      | 86           | 100    | 92      | 14.3            | 15.4   | 15.2    | 1.3           | 4.4    | 4.1     | 10           | 92     | 66      |
| 9-10          | JL      | 87           | 103    | 98      | 13.9            | 15.3   | 15.0    | 1.3           | 4.6    | 4.4     | 9            | 105    | 91      |
| 1-2           | CT      | 99           | 122    | 135     | 14.3            | 15.3   | 15.1    | 0.8           | 2.8    | 3.4     | 8            | 86     | 92      |
| 3-4           | CT      | 129          | 121    | 117     | 14.1            | 15.1   | 15.0    | 0.8           | 3.1    | 3.8     | 11           | 100    | 75      |
| 5-6           | CT      | 130          | 114    | 112     | 13.7            | 15.0   | 14.9    | 0.8           | 3.1    | 3.4     | 10           | 94     | 78      |
| 7-8           | CT      | 104          | 106    | 103     | 13.6            | 14.9   | 14.6    | 0.8           | 2.9    | 2.8     | 8            | 90     | 71      |
| 9-10          | CT      | 115          | 117    | 110     | 13.4            | 15.4   | 14.6    | 1.1           | 3.3    | 3.3     | 10           | 87     | 79      |
| 1-2           | DVR     | 94           | 114    | 113     | 14.0            | 15.3   | 15.0    | 1.1           | 4.0    | 4.7     | 8            | 90     | 63      |
| 3-4           | DVR     | 103          | 90     | 87      | 14.1            | 15.3   | 15.1    | 1.0           | 4.4    | 4.0     | 12           | 108    | 73      |
| 5-6           | DVR     | 90           | 99     | 90      | 14.3            | 15.4   | 15.0    | 0.9           | 4.0    | 4.0     | 10           | 90     | 76      |
| 7-8           | DVR     | 102          | 84     |         | 14.3            | 15.7   |         | 1.1           | 3.8    |         | 9            | 69     |         |
| 9-10          | DVR     | 85           | 100    | 95      | 14.2            | 15.4   | 15.1    | 0.9           | 3.1    | 3.3     | 11           | 90     | 80      |
| 1-2           | KB      | 109          | 119    | 108     | 14.8            | 16.1   | 15.7    | 1.3           | 3.7    | 3.8     | 12           | 110    | 111     |
| 3-4           | KB      | 100          | 112    | 102     | 14.5            | 15.7   | 15.6    | 0.9           | 4.2    | 4.0     | 11           | 95     | 96      |
| 5-6           | KB      | 97           | 113    | 108     | 14.7            | 16.0   | 15.7    | 1.2           | 4.2    | 4.0     | 11           | 94     | 88      |
| 7-8           | KB      | 114          | 110    | 117     | 14.6            | 16.0   | 15.4    | 1.0           | 4.5    | 4.3     | 10           | 98     |         |
| 9-10          | KB      | 80           | 108    | 105     | 14.5            | 16.2   | 15.0    | 1.1           | 4.1    | 4.5     | 13           | 116    | 91      |

Figures in boldface are those obtained during the period of daily administration of methyl testosterone.



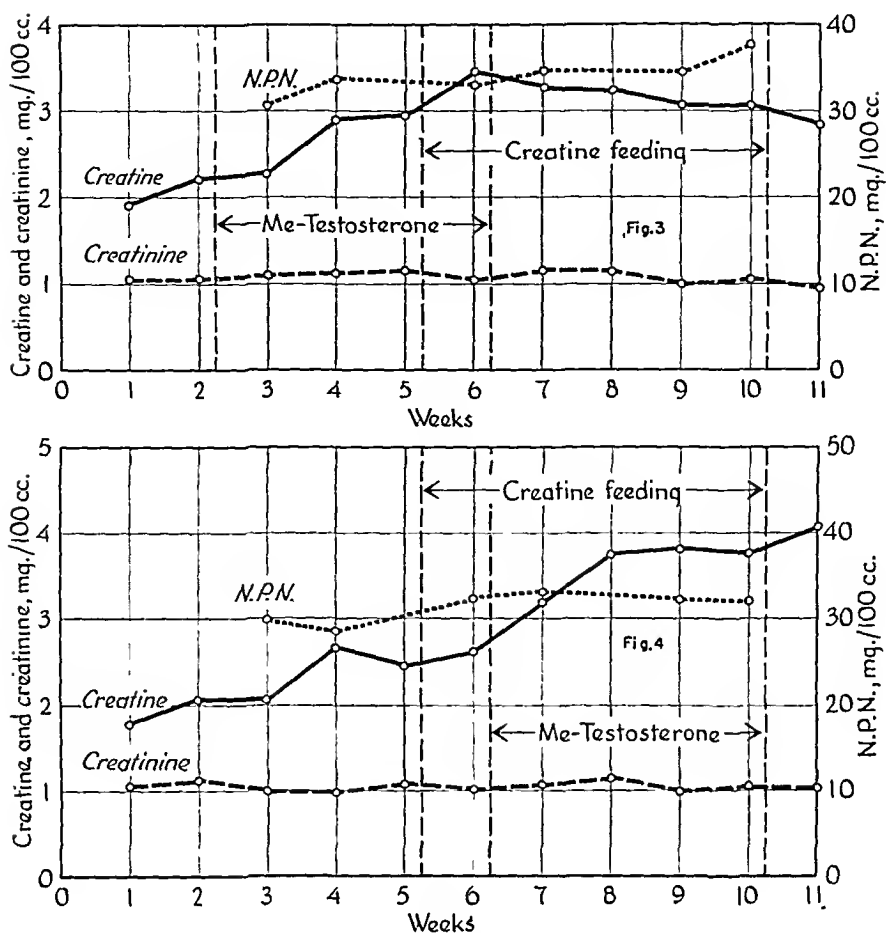


Fig. 3. BLOOD CREATINE, CREATININE AND NON-PROTEIN NITROGEN CONCENTRATIONS in subjects receiving methyl testosterone during the first part of the experimental period.

Fig. 4. BLOOD CREATINE, CREATININE AND NON-PROTEIN NITROGEN CONCENTRATIONS in subjects receiving methyl testosterone during the latter part of the experimental period.

extra creatine intake in itself did not provoke either creatinuria or creatinemia to any extent. So far as the data go it appears that the creatine ingestion had little or no effect on the concentration in either blood or urine. It may be noted that by the fourth week of administration of methyl testosterone the urinary output of creatine exceeded the extra creatine intake and that similar creatine output values were obtained whether creatine was fed or not.

Basal metabolism was substantially constant and was within normal limits at all times. With the exception of a single measurement on one subject all values on all 4 subjects were within the range  $-1$  to  $-10$  per cent in terms of normal averages for the respective ages and surface areas of the men, using the Mayo Clinic standards of Boothby and Berkson (10).

It is not necessary to present in detail the blood and urine concentrations of creatine, creatinine and nitrogen for the recovery period following the treadmill exercise. The results confirm the picture of moderate creatinemia and marked creatinuria obtained from the resting samples.

The rate of creatine output after exercise was reduced, as compared with that during rest, in all ex-

periments; the work-recovery values in individual experiments ranged from 18 to 79 per cent of the preceding output in rest, with a grand average of 45 per cent. On the other hand, the rate of excretion of creatinine in recovery was almost always increased, the grand average being 11 per cent greater than in rest before work. Likewise, the rate of total nitrogen excretion was increased following work, the grand average being 23 per cent above the values in rest before the work. However, none of these changes in recovery as compared with rest showed any tendency to be affected by the medication.

#### DISCUSSION

The four men, two castrates and two eunuchoids, studied by Simonson, Kearns, and Enzer (2) unquestionably improved in the physical tests during the period of administration of methyl testosterone. However, no adequate controls were provided, and the effects of learning and training could not be evaluated. Even if we agreed that methyl testosterone results in improved physical ability in cases of male hormone inadequacy (which is not proved), it would be uncertain what could be expected in normal men

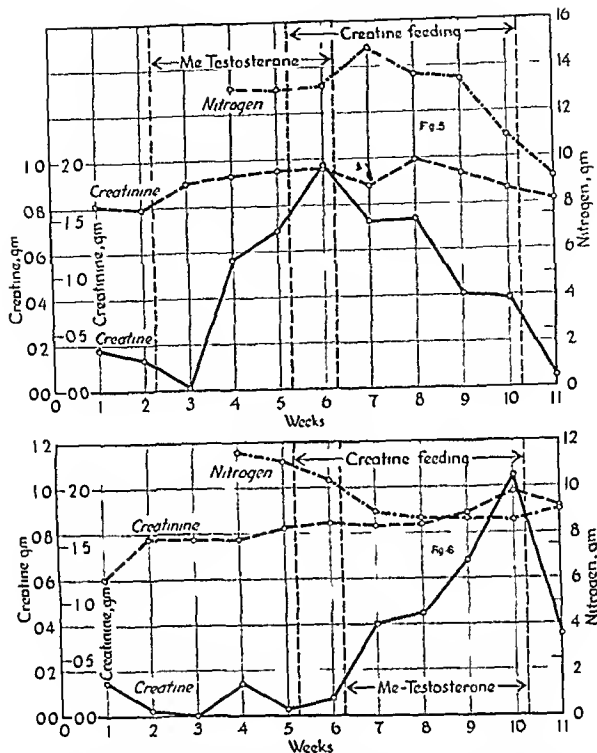


Fig 5 CREATINE CREATININE AND TOTAL NITROGEN EXCRETION IN THE URINE during rest, expressed as gm per day. Subjects receiving methyl testosterone during the first part of the experimental period. Averages for two subjects.

Fig 6 CREATINE CREATININE AND TOTAL NITROGEN EXCRETION IN THE URINE during rest, expressed as gm per day. Subjects receiving methyl testosterone during the latter part of the experimental period. Averages for two subjects.

from such medication. The present results indicate that no improvement is obtained with 50 mg of methyl testosterone daily. However, it is not impossible that somewhat different results would be observed with extremely large dosages, or with physical exercise which placed more emphasis on endurance.

The effect of methyl testosterone on creatine metabolism is of considerable interest. Increased nitrogen storage in dogs given testosterone was observed by Kochakian and Murlin (11). Similar effects in human beings were later reported by a number of workers, notably Kenyon et al (3) and Albright (16).

It has been assumed that much of the stored nitrogen finds its way to muscle protein, since potassium, phosphorus and water are also stored at the same time. The fact that creatine excretion is reduced under these circumstances in eunuchoids and castrated animals has also led to the belief that the nitrogen storage may be explained in this way.

Williamson and Gulick (5) studied the effect of testosterone propionate injections on the excretion of exogenous creatine by mature male rabbits. Creatine excretion was decreased but the blood level was constant. Paired muscle analyses indicated that, in fact, creatine storage in the muscles did take place so that the reduced excretion might be accounted for in this way. On the other hand the administration of testosterone propionate did not reduce the creatinuria of children (12), nor did it influence the exogenous creatine tolerance of old men (13).

The Jaffe reaction is notably non specific and we early considered the possibility that the increased 'creatinine' in our experiments might actually be some other compound. Attempts to prepare the DuBois enzyme failed owing to death of the bacterial culture. However, it was possible to rule out steroid substances as the active compounds. Aliquots of urines with high creatine titers were extracted with

ether both before and after autoclaving with acid. None of the active material could be extracted with ether in either case.

During the completion of the present work the paper of Wilkins, Fleischmann and Howard (14) appeared. They found that methyl testosterone provoked an exaggerated creatinuria in boys and girls suffering with pituitary deficiency; the creatine analysis was checked by the DuBos enzyme. This report adds weight to our belief that a true creatinuria was produced in our own subjects.

In our subjects there was no significant creatinuria normally. The creatine excretion attendant upon methyl testosterone administration apparently was not due to wasting of muscle because a), total nitrogen excretion was not increased, b), there was no loss of strength or of the body weight, c), there was no change in creatinine excretion such as is seen with muscle wasting in the muscle dystrophies. It would appear that there was an increased production of creatine. Further, by comparison with the other studies cited, it seems that methyl testosterone and testosterone propionate may have different effects on creatine metabolism.

There is no evidence that the creatinuria produced in our subjects by methyl testosterone was due to stimulation of the thyroid gland. McCullagh and Rossmiller (15) have reported that the basal metabolic rate was considerably elevated in patients after continued administration of large doses of this drug. They also found changes in carbohydrate metabolism characteristic of hyperthyroidism. Wilkins, Fleischmann and Howard (14) also found an increased metabolic rate associated with the creatinuria in their treated dwarfs. While we did not determine the metabolic rate of our subjects throughout the experiment, there was no significant difference during the last 3 weeks between the subjects receiving the drug and those receiving placebos. The low normal levels leave no reason to expect that any significant increase had occurred earlier in the experiment. The large excretion of creatine does not seem to be the result of changes in general metabolic rate.

Since creatine metabolism is intimately connected with the carbohydrate cycle in muscle, it is interesting to note that the changes in creatine output were unconnected with any changes in lactate or pyruvate production, or with blood sugar changes during exercise. If muscle phosphocreatine had been significantly changed, current theories would indicate that shifts in rate of phosphate exchange, and therefore of lactate and pyruvate production, would have resulted. Since this did not occur, it would appear

that the creatine changes after methyl testosterone are not due to any large shifts within the muscles themselves. The work of Borsook and Dubnoff (17), Baker and Miller (18) and Bodansky et al. (19) would indicate that creatine is largely formed in the liver and kidneys. It would seem, therefore, that a change in creatine metabolism in the liver or kidneys is the most probable effect of methyl testosterone.

#### SUMMARY

Administration of 50 mg. of methyl testosterone per day to 4 normal young men for periods of 3 and 4 weeks did not significantly change their grip strength nor alter the shifts in water, blood sugar, lactic acid and pyruvic acid produced by a period of short, intense exercise.

No significant changes in basal metabolic rate or in nitrogen output followed the treatment.

Administration of methyl testosterone was associated with a gradual increase of creatine excretion to relatively high levels. The creatinuria gradually decreased after cessation of treatment with the drug. There was an associated small increase in the blood creatine. Creatinine levels in blood and urine were unchanged.

The high creatinuria appeared to be unassociated with any evidence of thyroid stimulation or with any change in the carbohydrate metabolism of the muscles.

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# Clinical Reviews in Andrologic Endocrinology: II. Treatment of Androgenic Failure

[A Review Article]

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SEGREGATION of the various etiologic factors in hypogonadism as outlined in the previous paper (1) delineates a rational therapeutic approach and permits a definition of the prognosis. Pertinent information elicited from the history often establishes the existence of testicular failure, e.g., surgical extirpation of both testicles, failure induced by roentgen ray or radium, persistent non development or retarded maturation of the sexual system in patients of post adolescent or adult years and instances, wherein the presumptive diagnosis of testicular failure is ascribable to the metabolic alterations of senescence. The non existence of gonadal failure is apparent in instances of proven fertility. The ability to fertilize is the most reliable objective evidence of ample testicular function.

In the first paper of this series (1) it was emphasized that two grades of hypogonadism may exist, depending upon the time of onset of testicular failure, a), initial preadolescent or adolescent testicular failure, and b), adult or intercurrent testicular failure. The therapy of these two types of testicular failure is reviewed.

## THE THERAPY OF INITIAL OR ADOLESCENT TESTICULAR FAILURE

Adolescent testicular failure (characterized by varying degrees of genital hypoplasia, delayed puberty, anthropometric discrepancies involving non union of the epiphyses with resultant overgrowth of the long bones, peculiarities in body habitus ascribable chiefly to abnormalities in fat padding and decreased urinary titers of androgens) may be due to 5 causes a), inanition from dietetic discrepancies, or cachexia from acute and chronic debilitating diseases, b), childhood and preadolescent hypothyroidism, c), childhood and preadolescent diabetes mellitus, d), intrinsic testicular failure, and e), childhood

and preadolescent hypopituitarism. The diagnosis and treatment of the first three classes of causes is relatively satisfactory. Attention to the diverse extra-endocrine causes of testicular failure, e.g., correction of foci of infection, medical therapeutics of acute and chronic debilitating states, correction of anemia, restoration and stabilization of general body metabolism associated with obesity or leanness, often constitutes effective and rational therapy.

Differentiation between failure due to intrinsic testicular refractivity and that due to inadequate gonadotropic stimulation from the pituitary is somewhat difficult, inasmuch as adequate clinical evaluation of pituitary function is not possible by present diagnostic procedures. Occasionally, the endocrine survey may afford presumptive differentiation. Retardation of somatic growth may suggest pituitary deficiency, whereas statural overgrowth of the long bones, as evidenced by increased measurements of the span over the height and the lower measurement (from the symphysis pubis to the soles of the feet) over the upper measurement (from the symphysis pubis to the top of the head), implies no deficiency of growth hormone (pituitary) but suggests delayed epiphyseal closure ascribable to intrinsic testicular failure.

In the absence of clinical findings permitting these diagnostic departures, therapeutic trials with gonadotropic substances may complete the diagnosis, bearing in mind that the primary purpose of gonadotropic therapy of childhood and adolescent testicular failure is the circumvention of possible subsequent sterility. If the sole reason for gonadotropic therapy is the induction and maintenance of adequate androgenic function of the testes, the more practical, effective and economic therapy is by substituting or supplementing at the testicular level with androgenic preparations.

Hopes of therapeutic success with gonadotropins

in instances of childhood and adolescent hypogonadism assume that irremediable degenerative alterations in the seminal epithelium and interstitial cells of the testes have not occurred as the result of pituitary deficiency, and that adequate qualitative and quantitative gonadotropic therapy may be administered. Those patients giving desired clinical response to stimulation by gonadotropic therapy may be considered to have had deficient pituitary function, whereas those patients failing to respond to gonadotropic therapy may be assumed to manifest intrinsic testicular refractivity. In that connection, it must be recalled that those patients responding to gonadotropic therapy may effect ultimate gametogenic function whereas those patients requiring substitution therapy with androgenic substances, while anticipating recovery of the endocrine manifestations of the hypogonadal state, will not recover from the underlying seminal inadequacy.

A practical regime of gonadotropic therapy is as follows. *a)*, Pretreatment observations which should include those regarding the degree of sexual development with definite measurements of the penis, testes and evaluation of prostatic development; *b)*, roentgenologic surveys of osseous growth and epiphyseal development; *c)*, serial photographs of the growth responses of the external genitalia; and, if facilities permit, *d)*, laboratory data concerning the urinary excretion of androgens and 17-ketosteroids.

The initial trial of therapy is instituted with the chorionic gonadotropin because of its ability to stimulate the interstitial cells of the testes to produce greater quantities of androgenic steroids. Objective clinical observations concerning the response to therapy will be determined by evidences of increased androgen production, *i.e.*, the sexual development will reflect the levels of androgenic function. Having determined by preliminary skin tests that the patient is not allergic to the particular gonadotropic extract selected, intramuscular injections of 250 to 500 international units of one of the commercial preparations of chorionic gonadotropin should be administered daily for a period of 6 weeks. During therapy, weekly observations should note evidences of genital growth and, if possible, there should be studies of the urinary excretion of androgens or 17-ketosteroids which may be increased. If clinical data do not indicate the occurrence of specific testicular response at the end of 6 weeks of intensive therapy, dosages may be doubled and treatment maintained for another 6 weeks.

Patients failing to respond satisfactorily to this trial with gonadotropic therapy should be considered to have intrinsic testicular failure and the advisability of substitutional, androgenic therapy should be evaluated. In that connection, however, it should be recalled that the prognosis for ultimate gametogenic

function is poor. On the other hand, adequate androgenic therapy may induce sufficient sexual maturation and consequent development of testicular responsiveness that later trials with gonadotropic therapy may permit adequate functional development of both the endocrine and exocrine components of the testes.

In those patients responding satisfactorily to the initial gonadotropic therapy, treatment should be terminated in order to note the temporary or permanent character of the responses obtained. If sexual regression ensues, two methods of approach are available, *a)*, to give repeated courses of chorionic gonadotropin designed to maintain adequate androgenic levels; or *b)*, to maintain and promote sexual maturation and development with complemental androgenic therapy. The fact that androgens in maintenance dosages depress spermatogenesis in the adult should not discourage their clinical employment in these circumstances, for no evidence has been submitted that these depressing effects are permanent. Therapy by either of these modes should be continued until the testes are able to function spontaneously or until the need for evaluation of the seminal status becomes apparent. In the latter event, therapy as considered in the third paper of this series should be initiated (2).

Having considered the principles underlying the diagnosis and etiologic differentiation of childhood and adolescent testicular failure, a comprehensive analysis of its therapy may now be presented. From the foregoing discussion, it is apparent that two grades of adolescent testicular failure may exist, *a)*, genital hypoplasia associated with statural retardation; and *b)*, genital hypoplasia associated with statural overgrowth. The factual data supporting the therapy and prognosis for these two forms may be presented briefly.

#### GENITAL HYPOPLASIA WITH ACCOMPANYING STATURAL RETARDATION

As indicated above, therapy may be stimulative, (gonadotropic) or substitutional (androgenic) in character, the response to gonadotropic preparations defining the indications for continuation of stimulatory therapy.

#### Gonadotropic Therapy

In the choice of gonadotropic substances one considers *a)*, the available commercial preparations of the anterior pituitary gland, the results with which have been generally conceded to be disappointing, and *b)*, those preparations obtained from pregnancy urine and pregnant mare serum.

The therapeutic efficacy of growth hormone (anterior pituitary preparation) has yielded conflicting data. Engelbach (3, 4) and his group reported beneficial results from therapy with growth hormone in

7 patients having genital hypoplasia and statural retardation. Moderate improvement in general growth after therapy with growth hormone was observed by Evans, Meyer, Simpson and Reichert (5), Shelton, Cavanaugh and Evans (6), Turner (7) and Lawrence and Harrison (8). Further analysis, however, of the clinical responses to growth hormone by Shelton, Cavanaugh and Evans (9) yielded disappointing results. Our results with growth hormone have not been encouraging.

The majority of the reports of stimulative therapy for hypogonadism and statural retardation are concerned with the therapeutic efficacy of the chorionic gonadotropin. Sexton (10) reported little success from therapeutic employment of pituitary gonadotropic hormone. Our group likewise has observed no stimulation of growth in 3 patients manifesting genital hypoplasia and statural retardation which were treated with pituitary gonadotropic factor. The observations of Dorff (11-17), Thompson and his group (18-21), Sexton (10), Lichtwitz (22), Schaefer and Kitchen (23), Turner (24) and Mimpriss (25) indicate that therapy of adolescent testicular failure with chorionic gonadotropin results in diverse effects. These are a), growth and development of the sexual system as manifested by the appearance of suprapubic hair, enlargement of the penis and scrotum, increased frequency of erections and 'break' in the voice; b), increased increment of growth as evidenced by marked spurt in height and osseous development, although evidence that premature epiphyseal closure may result from therapy is lacking; and c), redistribution of fat (10) in instances of adiposogenitalism.

Precocious sexual development may result from too enthusiastic or too prolonged therapy with the chorionic gonadotropin, hence it is advisable to note the rate of genital growth periodically during the course of therapy. Discontinuation of therapy prior to adolescence results commonly in partial regression of the genital growth induced by therapy. Unlike therapy with the pregnant mare serum gonadotropin (26, 27), prolonged therapy with chorionic gonadotropin does not evoke antibody formation (11-17, 28, 29) which tends to inhibit testicular activation. Adequate evidence has not been submitted (30) that the chorionic gonadotropin may effect degenerative changes in the testes. Kunstader (31) has reported definite genital growth and sexual maturation in a group of 14 boys treated with 10 to 20 Cartland-Nelson units of equine gonadotropin 3 times weekly for several weeks.

Considerable difference of opinion exists concerning the optimum time for institution of gonadotropic therapy in instances of adolescent testicular failure, especially in those cases thought to be adiposogenitalism. Dorff (11-17) believes that therapy should be

initiated not earlier than 5 years and not later than 13 years. On the other hand, considerable evidence has been submitted by Ellis and Tallerman (32), Gray (33), Bruch (34) and Werner (35) that many instances of genital hypoplasia ascribable to adiposogenitalism will progress normally to puberty without therapy other than dietary restriction. Werner (35) believes gonadotropic therapy designed to effect the sexual and statural alterations of puberty should not be considered prior to 16 years of age, except in those instances wherein severe psychological difficulty results from genital and statural underdevelopment.

### *Androgenic Therapy*

Substitutional therapy with available commercial preparations of androgenic substances is indicated in those instances of genital hypoplasia and statural retardation which fail to respond to stimulative therapy with gonadotropic preparations. Many data have accrued concerning the efficacy of androgenic therapy in hypogonadism, the criterion of production of genital growth being accepted generally, whereas the responses of somatic growth to androgenic therapy are regarded not without equivocation. Diverse routes of administration of androgenic substances have been employed, a), intramuscular, b), oral, c), percutaneous and d), implantation of crystalline pellets. Most of the reports predicate the employment of androgenic preparations in adolescent testicular failure upon one or more of the following results obtained: a) development and maturation of the sexual system; b), production of somatic growth; and c), an undetermined rôle of psychological stabilization and metabolic alterations resulting in increased vigor and activity and aggressiveness.

As stated above, therapy with androgenic preparations may include intramuscular administration of testosterone propionate, oral therapy with methyl testosterone or testosterone propionate (accepted generally as being ineffective by mouth), inunction with ointments containing testosterone propionate in a lanolin petrolatum base, and implantation of pellets of crystalline testosterone or methyl testosterone. Selection of the therapeutic regime is determined by the availability of the products, estimation of the need for prolonged therapy and the cost. Exhaustive reviews of androgenic principles have been submitted by Koch (36-39), Vest and Howard (40), Moore (41) and Hamilton (42).

*Production of genital growth.* Clinical reports attesting the induction of genital growth following intramuscular therapy with testosterone propionate have been reported by Kenyon and his group (43-47), Hamilton (42, 48), McCullagh and his coworkers (49-53), Foss (54), Morigard and Bize (55), Vest and Howard (40, 56), Riches (57), Walther and Willough-

by (58), Nathanson and Towne (59), Ketcham (60), Turner (61), Kearns (62), Dunn (63), Moehlig (64), Aub (65) and others. Dependent upon the severity of the testicular failure, the dosages of testosterone propionate usually employed are 25 mg. 3 times weekly, or more often, until the desired genital growth has resulted; thereafter the dosage is reduced to maintenance levels of 10 mg. 3 times weekly or more often.

The intramuscular administration of testosterone propionate to the hypogonadal male effects characteristic responses (41, 42, 49-53, 59) which may be considered briefly.

a) Alterations in the blood volume and pigmentation of the skin (66, 67) occur within an hour following injection. Simultaneous with the increase in blood volume (occurring generally throughout the body, except in the buttock) and of the percentage of hemoglobin, there is an increase, although to a lesser degree, of melanin and related substances. As a result, the pallor and waxy appearance of the skin of the hypogonadal individual is replaced by flushing and deepening of color.

b) Appearance of spontaneous erections and increase in the erectile power may ensue within several hours.

c) Increased excretion of urinary androgens (49-53, 59, 68-74) occurs within a few hours following injection of testosterone propionate with a slow return to normal levels within 48 hours, although the androgen excretion may be increased for several days. These increases may be related to increased excretion of androsterone, a product of testosterone metabolism, although the recovery of the active substance varies from 14 to 70 per cent, the fate of the remainder being unknown. Clinical data (49-53, 68-71) suggest that maintenance of the level of urinary androgens within the range of normal is evidence that ample testosterone has been administered to effect the desired clinical responses.

d) The appearance of the secondary sexual hair follows within a few weeks, axillary and pubic hair being the first to grow. The beard, too, becomes stiffer and coarser. After several weeks of therapy, hair appears on the trunk and limbs. Increased oiliness of the skin may result and the appearance of acneiform responses may ensue.

e) Genital enlargement and development occurs likewise within a few weeks. The penis undergoes considerable growth, the scrotum manifests proportionately less growth and development of the prostate is perceptibly slower. Nocturnal emissions may be experienced and the quantity of the semen is considerably increased. Inadequate clinical evidence exists to support the assumption that testicular growth may be stimulated by androgenic therapy, although Webster (75) reported testicular growth in 3 hypogonadal boys treated with androgens.

f) Deepening of the voice is a characteristic alteration ascribable to androgenic therapy. This may be related to congestion and roughening of the mucous membrane of the larynx (42) or to alterations in growth of the tracheal or laryngeal cartilages.

g) Increased body weight and diverse metabolic alterations may be induced by androgenic therapy. The studies

of Kenyon and his group (43-47) have suggested that the gain in weight may be ascribable to retention of water, electrolytes and nitrogen resulting from androgenic therapy, a finding comparable to similar phenomena produced by adrenal cortical substances (76-81) except for the fact that hypogonadal males treated with testosterone propionate manifest diminished urinary potassium excretion (43-47) whereas patients with cortical adrenal failure treated with adrenal steroids show increased urinary potassium excretion. The various metabolic alterations (43-47) in the hypogonadal male treated with testosterone propionate may be summarized as: a reduction in the volume of urine; retention of 1 to 4.5 gm. of nitrogen daily as reflected by uniform decline in urinary nitrogen in the form of urea, the urinary creatinine being unaffected (42, 43-47); no alterations in the nitrogenous components of the blood; retention of 0.33 to 0.55 gm. of sodium and a proportional retention of associated chloride ascribable to decline in urinary sodium and chloride excretion (42, 43-47); slight decline in urinary sodium and chloride excretion; slight decline in urinary potassium excretion; considerable reduction in urinary inorganic phosphorus excretion; no significant alterations in serum lipid values (82); minimal or no alteration in the basal metabolic rate, the fasting respiratory quotient, pulse rate and blood pressure. The retention of nitrogen and proteins throughout the body generally permits explanation of the unusual somatic growth accompanying precocious adolescence, i.e., androgenic therapy designed to stimulate genital growth may effect diverse somatotrophic influences (43-47).

h) Alterations of osseous development, i.e., premature or advanced epiphyseal closure, have been related to androgenic therapy both by animal experiments (83, 84) and by clinical observations of Howard and Vest (56) and McCullagh and McGurl (85). The question remains equivocal, however, inasmuch as other studies (75, 86-90) have not confirmed this observation.

i) Nelson (91, 92) has observed favorable alterations of cardiac output in hypogonadal males treated with androgenic preparations.

Therapy of hypogonadal males with androgenic substances has resulted in various complications. a) Edema of the lower extremities, especially the ankles, has resulted from over-enthusiastic therapy with testosterone propionate (93). b) Bilateral gynecomastia has resulted from therapy with either testosterone propionate or methyl testosterone (94), suggesting, therefore, that these androgens may exert specific stimulating effects upon breast tissue. c) Annoying frequency of erections, which may result in priapism unrelieved by intercourse (54) has been observed. Reduction in dosage of testosterone propionate usually effects relief. d) Excessive genital growth may be induced by prolonged therapy (95, 96) in instances of adolescent testicular failure, the precocious development and other evidences of maturity defining the need for cautious therapy of young boys with androgenic preparations. On the other hand, Ehrenstein (97) and Kunstadter (95) warn that possible gonadal

damage may follow androgenic therapy e) The question of possible premature epiphyseal closure secondary to androgenic therapy has been discussed. f) The production of acneiform responses (49-53) by androgenic therapy constitutes an annoying complication g) The studies of Moore (98), Heekel (99) and McCullagh and McGurl (49-53) have demonstrated that spermatogenic function is impaired by androgenic therapy, although Rubinstein and Kurland (100) report increased spermatogenesis with small dosages of 5 mg of testosterone propionate 3 times weekly

Due, perhaps, to inactivation by the liver (101, 102), the oral administration of testosterone propionate has proven ineffective clinically (68-71) Based on the animal experiments of Miescher and Tschopp (103) and Emmens and Parkes (104), Foss (54, 105-108) employed methyl testosterone orally in the therapy of hypogonadal males and obtained evidence of favorable androgenic responses These observations have been confirmed by Loesser (109, 110), McCullagh (111), Dorfman and Hamilton (68-71), Kearns (112), Tager and Shelton (113) and Byron and Katzen (94) The maximum oral dosage has been accepted generally to be 100 mg daily, which is taken commonly as 4 divided doses when the stomach is empty The medication is followed by one half glass of warm water to insure maximum absorption In that connection, the administration of bile acids by mouth is said to enhance considerably the oral effectiveness of androgenic substances (114-119) The maintenance dosage of methyl testosterone is considered to be 50 mg daily, denoting, therefore, a dosage requirement 4 to 6 times greater than that of intramuscular testosterone propionate Minimal toxicity to methyl testosterone orally has been experienced in the form of slight nausea, anorexia and gastric irritation which is relieved by alkaline mixtures A possible explanation for the oral effectiveness of methyl testosterone as compared to testosterone propionate has been advanced by Biskind (101) His experiments suggest that methyl testosterone is absorbed from the gastrointestinal tract through the lacteals and lymphatics rather than the portal circulation, avoiding, thereby, immediate inactivation by the liver The results following administration of methyl testosterone orally differ from those following intramuscular testosterone propionate in three ways a) Clinically effective doses of methyl testosterone produce no increase in urinary androgenic excretion (68-71, 111) whereas pronounced increases follow therapy with testosterone propionate b) Prolonged therapy with methyl testosterone orally requires gradual increases in dosage to maintain clinically effective levels (94, 111) McCullagh (111) suggests that this may be related to an increased ability of the

liver to metabolize methyl testosterone c) Slight elevation of the basal metabolic rate has been observed (94, 111) following therapy with methyl testosterone whereas little or no alteration in the basal metabolic level is induced by therapy with intramuscular testosterone propionate (43-47) The chief objection to clinical employment of methyl testosterone is the cost of the preparation

The effectiveness of the percutaneous employment of testosterone propionate in the therapy of diverse grades of hypogonadism has been demonstrated by Moore, Lamar and Beck (120), Foss (105-108), Kearns (62) and Tager and Shelton (113) An effective daily dosage may be considered to be 14 mg of active principle (113) in 7 gm of petrolatum lanolin base, although Foss (105-108) observed that the dosage of testosterone propionate by injection is two or three times the effective intramuscular dosage.

In instances wherein prolonged and uniform therapy with androgenic preparations is desirable, the advisability of intramuscular implantation of pellets of crystalline androgenic substances may be considered. Favorable responses in the therapy of hypogonadal males with implantations of pellets of pure testosterone have been observed by Deane and Parkes (121, 122), Howard and Vest (56), Vest and Howard (123), Hamilton and Dorfman (124), Foss (105-108), Eidelsberg and Ornstein (125) and Biskind and his group (126-128) Hamilton (42) recommends intramuscular implantation of 960 mg. of testosterone divided between 4 pellets, each of which is 5 mm in diameter and 7 mm in length Biskind and his co-workers (126-128) prefer methyl testosterone rather than testosterone, inasmuch as the high melting point of methyl testosterone permits sterilization of the pellets in the pressure autoclave whereas the pellets of testosterone are considerably more difficult to sterilize They estimate the effective clinical dosage of methyl testosterone to vary from 2 to 3 mg daily, indicating, therefore, that approximately one-fifth of the daily maintenance dosage of injected testosterone propionate is required by the implantation method

Inasmuch as therapy of hypogonadal states with androgenic preparations is substitutional in character, therapy must be continued at maintenance levels sufficient to effect the desired clinical responses Eidelsberg and Ornstein (125) observed no ill effects with prolonged androgenic therapy other than too frequent erections and increased libido Withdrawal of therapy effects diverse alterations (49-53) such as prompt diminution in libido and erectile power, pronounced reduction in the volume of the seminal fluid ascribable to decreased prostatic and vesicular secretion, atrophy of prostate and seminal vesicles, minimal or no regression of the external genitalia, and



no alterations in the distribution of sexual hair, skeletal maturation and laryngeal growth.

Therapy of adolescent testicular failure oftentimes may be discontinued when clinical responses denote the development or recovery of testicular function. This may be judged by *a*), development and maturation of the sexual system; *b*) recovery from diverse extra-endocrine factors attributable to testicular failure; *c*), rational therapy of various endocrinopathies such as hypothyroidism and diabetes mellitus; *d*) surgical and medical therapeutics of various urologic diseases; *e*), an induction of adequate genital growth by androgenic therapy so as to permit response to gonadotropic therapy and *f*), sufficient modification of skeletal growth by androgenic therapy so that indications for further treatment are non-existent.

*Alterations of somatic growth.* Although the clinical observations of Howard and Vest (56) and McCullagh and McGurl (85) suggest that prolonged therapy with androgenic principles may permit advanced epiphyseal closure, reports concerning the stimulation and production of statural growth by androgenic therapy have been submitted by Webster (75, 87, 88) Villaret, Justin-Besancon and Rubens-Duval (86), Moricard and Bize (89) and Rapfogel (90). Webster (75, 87, 88) administered intramuscularly 75 to 125 mg. of testosterone propionate weekly to 8 hypogonadal boys ranging in age from 9 to 18 years, observing an increase in the rate of growth from 1.36 centimeters per 100 days during the control period to 3.6 centimeters per 100 days during the treatment period. Upon discontinuation of therapy, the average growth rate decreased to 1.56 centimeters per 100 days. Webster (75, 87, 88) has stated that the mechanism of the growth spurt following androgenic therapy is obscure, although it may be related to indirect alterations mediated via the pituitary. Kenyon (43-47) suggests that the retention of nitrogen and proteins generally throughout the body may be related to diverse somatotrophic influences of androgenic substances.

Our group, likewise, has observed stimulation of statural growth induced by therapy with testosterone propionate in 5 patients ranging in age from 15.5 to 19 years. Three patients received 10 mg. doses of testosterone propionate thrice weekly, the growth responses during therapy being 1.38 inches in 193 days, 1.5 inches in 64 days and 2.0 inches in 151 days, respectively. Although the bone age of all 3 patients was retarded 2 or 3 years, no advancement of bone age occurred during therapy. The remaining 2 patients were treated with 25-mg. doses of testosterone propionate thrice weekly, the growth responses being 1.25 inches in 2 months and 1.5 inches in 11 months, respectively. Epiphyseal closure, how-

ever, was markedly accelerated by doses of 25 mg. of testosterone propionate thrice weekly, the bone age apparently being advanced 4 years in one patient treated for 11 months and 2 years in the other patient, treated for two months.

*Stabilization of psychological reactivity.* In instances of adolescent testicular failure wherein persistence of genital hypoplasia or altered statural growth induce diverse alterations of psychological responsiveness, therapy of the hypogonadal state, either of a stimulative or substitutional character, is advised (42). This does not suggest, however, the inference that alterations in testicular function are related directly to the psychological constitution of the individual.

#### GENITAL HYPOPLASIA ASSOCIATED WITH STATURAL OVERGROWTH

The development of testicular failure during the preadolescent epoch, *i.e.*, prior to the closure of the epiphyses of the long bones, results oftentimes in marked overgrowth of the long bones, as evidenced by increase of the lower measurement (from the symphysis pubis to the bottom of the feet) over the upper measurement (from the symphysis pubis to the top of the head) and increased measurement of the span over the height. In the choice of a rational therapy with androgenic principles one should consider not only the correction of the genital hypoplasia but the curbing of the osseous growth (56, 83-85) to prevent the cosmetic inelegance. That epiphyseal closure, perhaps, may be induced by therapy with doses of 25 mg. of testosterone propionate thrice weekly has been indicated above.

#### THERAPY OF ADULT OR INTERCURRENT TESTICULAR FAILURE

Intercurrent androgenic and seminal failure of the adult produce regressive alterations in the sexual system with little or no change in skeletal growth. The clinical observations denoting adult testicular failure include *a*), evidences of testicular atrophy or decrease in testicular firmness; *b*), marked depression of seminal values; *c*), decrease in the size of the prostate and seminal vesicles; *d*), decreased *libido sexualis*; and *e*), androgenic values of urine which may be lower than normal, but which frequently are normal or even higher than normal. The etiologic factors underlying adult testicular failure are identical with those attributed to adolescent testicular failure: *a*), extra-endocrine factors, such as inanition and cachectic states resulting from acute and chronic diseases; *b*), adult hypothyroidism; *c*), adult diabetes mellitus; *d*), intrinsic testicular inadequacy; and *e*), adult hypopituitarism. The diagnosis and treatment of the first three classes of causes, *i.e.*, the extra-endocrine

factors, thyroid deficiency states and diabetes mellitus, is relatively satisfactory. The differentiation of the last two classes, i.e., adult testicular failure due to intrinsic testicular non-responsiveness or to inadequate stimulation by the pituitary, if not permitted by the history and the endocrine survey, may require consideration of receptivity of the gonads to stimulative (gonadotropic) therapy as outlined in the following paragraphs.

Clinically, most cases of intercurrent androgenic and seminal failure of the adult are ascribable to causes intrinsic to the testes and are not associated, therefore, with hypogonadotropic functions of the pituitary. Moreover, it is unlikely that the most potent gonadotropins are capable of re-instituting normal function in testes subjected to diverse forms of destruction. Our experience with intensive therapeutic schedules of chorionic gonadotropin, alone or in combination with one another, or with testosterone propionate, in the therapy of seminal inadequacy has been disappointing. If gonadotropic therapy of germinal failure proves unsatisfactory, therapy of the androgenic deficiency states by substitution at the testicular level with androgenic steroids is the treatment of choice, providing, of course, that indications exist for androgenic therapy.

If a therapeutic trial of gonadotropins seems indicated under these circumstances, a suggested schedule of treatment is as follows. Pretreatment observations include careful evaluations of the seminal fluid (with reference to volume, number of spermatozoa per cc. of fluid, motility, percentage of abnormal forms and estimations of viability) secured after periods of established continence (i.e., after 7 days) and, if facilities permit, determination of the values for urinary androgens. Having determined the non-existence of possible allergy by preliminary skin-testing, dosages of 500 international units of one of the commercial preparations of chorionic gonadotropin are injected daily for a period of 6 weeks. During the last week of therapy or at its immediate termination, estimation of the therapeutic results is determined by repeated seminal studies, alterations in the prostate, seminal vesicles and consistency of the testes and androgenic values of the urine. If the testes respond to this form of therapy, increases in androgenic urinary titers should be noted, although significant alterations of seminal values will not be anticipated with the exception of those alterations which are affected by improved androgenic function. The rationale of this form of therapy is to stimulate if possible an increased production of androgens and affect, thereby, androgenic 'priming' of the male genital system before therapeutic attempts to stimulate spermatogenesis are initiated.

Both androgenic and germinal failure exist in these

patients and no clinically effective pituitary gonadotropin is available, so that in attempted therapeutic stimulation of spermatogenesis one should probably employ both chorionic and equine gonadotropin; the use of a preparation of 'pituitary synergist' and chorionic gonadotropin<sup>1</sup> also may permit satisfactory therapy in these cases. As in the preceding therapeutic schedule, pretreatment observations include seminal studies and androgenic determinations. (Those determined at the conclusion of the initial therapy with chorionic gonadotropin are satisfactory.) Immediately following the 6 weeks of therapy with chorionic gonadotropin previously described, combined gonadotropic therapy is instituted according to the following schedule. When preliminary skin-testing with each gonadotropic preparation is completed, dosages of 500 international units each of chorionic gonadotropin and equine gonadotropin or of 30 'synergy' units of the preparation of pituitary synergist and chorionic gonadotropin are injected intramuscularly daily for a period of 4 to 6 weeks. At the conclusion of this therapeutic schedule, evaluation of the treatment is determined by repeated seminal studies and determination of the androgenic values will indicate the occurrence or non-occurrence of specific responses. Further similar studies should be made 4 to 6 weeks following discontinuation of therapy in order that delayed responses may not be overlooked.

In those patients failing to respond to this form of treatment it is doubtful that further gonadotropic therapy will prove satisfactory. On the other hand, additional series of therapy as outlined above with adequate rest periods may be given to those patients effecting satisfactory responses.

Having considered, therefore, the principles underlying the diagnosis of the etiology of the adult testicular failure, it will be noted that the therapy for androgenic and seminal deficiency in the adult embraces commonly three chief purposes: a), initiation or restoration of gametogenic responses compatible with the fertile state, b) prevention of regressive alterations in the sexual system which may diminish the potentia coeundi of the hypogonadal male or effect diverse psychological maladjustments, and c), therapy of metabolic alterations resulting in diminished energy production by the hypogonadal individual.

It is apparent that the circumvention of existing sterility is the paramount indication for therapy of adult testicular failure. The correction of seminal failure is permitted only by the development of intrinsic testicular receptivity to gonadotropic stimulation. In instances wherein gonadotropic therapy is ineffective and recourse to substitutional therapy,

<sup>1</sup> One such preparation is prepared by Parke, Davis and Company, Detroit, Mich. (Synapoidin).

according to the schedules described above, is indicated, recovery of the seminal function, i.e., fertility, cannot be anticipated. Oftentimes, however, androgenic therapy may maintain the sexual system in a state of receptivity while local pathologic processes are subjected to indicated therapies, recovery from the intrinsic testicular failure permitting the return of responsiveness to gonadotropic activation.

The relationship of diverse grades of adult testicular failure, as manifested by varying degrees of regression of the sexual system, to psychological instability remains unsettled. Miller, Hubert and Hamilton (129), Dunn (63), Werner (130), Sharpey-Schaefer (131), Thomas and Hill (132) and Daniels and Tauber (133) have observed improved psychological adjustment in hypogonadal males following androgenic therapy. These studies, however, do not permit correlation with the physiologic epoch of testicular failure, i.e., the preadolescent period, wherein psychological alterations attributable to androgenic deficiency are non-existent. Furthermore, the various psychologic maladjustments of hypogonadal males cannot be segregated from latent imbalance of the autonomic nervous system aggravated by alterations in neuro-endocrine sympathies.

The studies of Lipross (134), Papanicolaou and Falk (135), Hesser, Longworthy and Vest (136), and Simonson, Kearns and Enzer (137) suggest relationship between muscular development and performance and intrinsic androgenic levels. Further observations concerning the mechanism of increased energy production induced in hypogonadal males by androgenic therapy are indicated before pertinent conclusions may be formulated.

#### SUMMARY

1. The ultimate aim of therapy of testicular failure is development of or restoration of fertility.
2. Rational therapy of testicular failure is determined by the diagnosis of and the degree of testicular impairment and differentiation of the etiologic factors contributing to testicular failure.
3. The various causes of testicular failure have been classified and the mechanism of their impairment of testicular function has been discussed.
4. The cause of testicular failure determines the prognosis relative to physiologic recovery and defines the therapeutic approach.
5. Diagnostic procedures to determine testicular responsiveness to gonadotropic therapy permit differentiation of testicular failure ascribable to intrinsic refractivity of the testes and defines the conditions for androgenic therapy. The procedures and interpretation of these therapeutic tests have been considered.
6. The limitations and procedures of various ther-

apeutic measures available at present for therapy of testicular failure have been discussed.

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# COMMUNICATIONS TO THE EDITORS

## Vasomotor Effects of Progesterone

SEVERAL YEARS AGO during an investigation<sup>1</sup> of the urinary excretion of sodium pregnanediol glucuronide following intramuscular injection of progesterone in sesame oil into volunteer members of a group of males, one of us (D. V. H.), experienced some subjective symptoms which were related theoretically to vasomotor effects of this hormone. In view of the fact that experimental studies upon laboratory animals have

and it was judged to be associated too closely with the progesterone therapy to be entirely incidental. That these symptoms were not without foundation was apparent from a concomitant fall in pulse rate and blood pressure. Resting pulse rates were recorded which were as low as 42 per minute while the blood pressure fell to 84 mm. Hg systolic, and 44, diastolic. These values were far below the individual's normal levels.

Some weeks later, the experiment was repeated after a record of the normal blood pressure and pulse rate had been made. The vasomotor effects of progesterone are presented in figure 1. The blood pressure fell dramatically and did not return to normal levels for 12 days. Intramuscular injections of similar amounts of sesame oil without progesterone, however, produced similar vasomotor changes. This fact has been observed also in experimental animals,<sup>2</sup> but there were enough differences between the results following injections of the oil and these following injections of oil and progesterone to indicate a possible specific vasomotor effect of progesterone.

Our plans to extend these clinical studies and to investigate in experimental animals the effects of progesterone given intramuscularly in non-vegetable oil vehicle (propylene glycol) were interrupted. Subsequently, however, it has been shown<sup>3</sup> that the intraperitoneal administration of progesterone to rats in dosages varying from 17 to 22 mg resulted in appreciable decreases in systemic blood pressure. On the other hand, it has been reported that the intravenous administration of  $\alpha$ -estradiol to dogs failed to effect any significant alterations in blood pressure.<sup>4</sup>

This personal observation by us suggests that clinical studies of vasomotor responses of males and females following implantation of crystals or pellets of progesterone might yield interesting and significant data upon this supposed effect of progesterone.

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<sup>2</sup> PARTINGTON, P. G., AND I. T. NATHANSON *Endocrinology* 25: 73. 1939.

<sup>3</sup> FRIEDMAN, S. M.: *Proc. Soc. Exper. Biol. & Med.* 46: 197. 1941.

<sup>4</sup> DICK, M., AND C. W. HOOKER. *J. Lab. & Clin. Med.* 25: 33. 1939

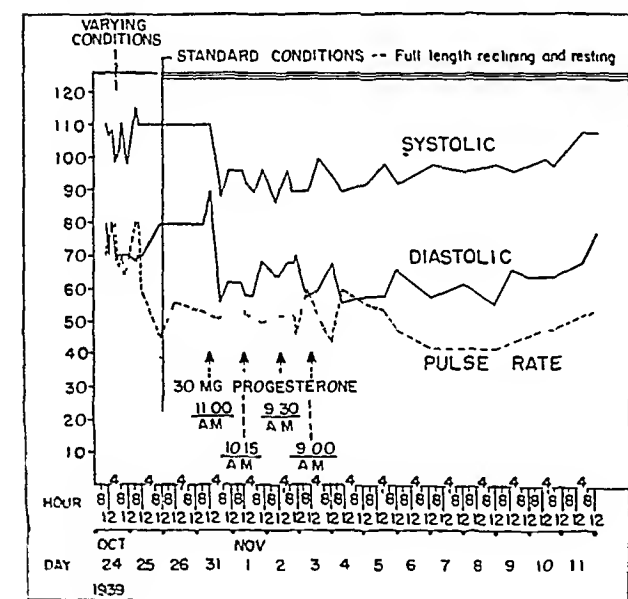


Fig 1. DAILY RECORDINGS of blood pressure and pulse rate of one of us (D. V. H.) before, during and following the intramuscular administration of progesterone in oil, 30 mg. daily for four days.

indicated that progesterone may influence the vasomotor system, and despite the fact that our clinical observations concern only one individual, it seemed advisable to report these findings.

During the course of daily intramuscular injections of 30 mg. of progesterone in sesame oil\* (10 mg. to 1 cc. of oil) for 4 days, D. V. H. experienced a sudden onset of an acute depression, with psychomotor retardation and associated feelings of impending calamity. These symptoms lasted throughout the 4-day period of treatment and for about 2 days thereafter. The experience was unique

<sup>1</sup> HAMBLIN, E. C., W. K. CUYLER AND D. V. HIRST: *Endocrinology* 27: 172. 1940.

\* Proluton and sesame oil supplied by Schering Corporation, Bloomfield, N. J.

# Androgenic Therapy in Women

## TO THE EDITOR

IN a recent letter to the Editor<sup>1</sup> Dr E C Hamblen sharply condemns the use of androgens in the practice of gynecology. He bases his discussion upon a particular case that came to his attention, one in which a total of 2500 mg of testosterone propionate was administered by some physician over a period of 10 months to a girl of but 15 years of age. This was truly an astonishing procedure.

One point which is fundamental and with which none will take issue is that the excessive use of any pharmacologic agent, hormonal or otherwise, is harmful. It must be admitted that following large parenteral doses (500 to 600 mg per month) of testosterone propionate, undesirable side-reactions such as temporary virilization may develop. Such dosage used parenterally has given cause for protestation that androgens are 'contrasexual'. But it will be that it is the dosage and not the hormone that is contraphysiologic. The administration of such massive doses as 2500 mg of testosterone propionate to a 15-year-old girl or of 500 to 600 mg per month to adults is contrary to good judgment or experience. These are very massive doses and in themselves do not constitute *a priori* arguments against the use of pharmacologically effective doses of androgens in gynecologic therapy. One can not logically argue against the use of any agent from the results of its abuse.

Are androgens contrasexual? Androgens presumably must play some rôle in the physiologic economy of the female, otherwise how can we account for the appearance of the same two androgens in the urine of normal women as have been identified in the urine of normal males (the Callows, Womack and Koch)? Likewise, estrogens are found in the urine of males, in fact, paradoxical as it may seem, an excellent source of certain estrogens is the urine of the stallion.

Is there a hypo androgenic state in the female? Doctor Hamblen perhaps rightly questions the existence of a hypo androgenic state which will justify the use of androgenic therapy in the female. However, his assumption that that might be the reason for its use by clinicians is entirely gratuitous. Epinephrine is useful in asthma in spite of the fact that a deficit of epinephrine has never been proven to exist in asthmatic patients. The use of androgens, therefore, does not imply an androgen deficit or hypo androgenic state, but rather that its use at times is expedient.

Are androgens ovary negating? The voices that have been raised against the use of androgens in the female arise from the concept that gonadal hormones should be sex specific and the observation that defeminizing and ovarian negating effects are produced by androgens following massive parenteral dosage. The parenteral use of massive doses of testosterone propionate in the female is contraphysiologic and ovary-negating. The use of comparatively large dosages of estrogens is also ovary negating. The ovary-negating effects which may be obtained with estrogens or androgens are mediated through the hypophysis by inhibition of the follicle stimulating hor-

none. Pharmacologically effective doses of testosterone propionate, which are far below the virilizing level, have been employed in several hundred cases by our group; therapeutic effectiveness has been the result in a goodly number of cases. When such dosage proved therapeutically ineffective the administration of the hormone was discontinued rather than increased. In more than 100 patients pellets were introduced in doses of 25 to 400 mg and in not one single instance was masculinization induced. It is true that Locser<sup>2</sup> observed transitory signs of masculinization in every one of 8 patients in his series. However, he used dosages of 600 to 1650 mg. An evaluation of our results indicated that pellet implants of testosterone propionate in doses as large as 400 mg were capable of alleviating many aberrations of gynecic function without any indication of suppression of hypophyseal-gonadotropic function or interference (antagonism) with the action of endogenous estrogen or progesterone on the uterus and vaginal mucosa. Ovulation, periodic follicle maturation, and glycogen desposition in both secretory endometrium and vaginal mucosa was not interfered with in cyclically functioning women. Furthermore, in menometrorrhagia, the therapeutic results could not be ascribed definitely to the influence on the hypophysis or ovary, since the endometrial pattern, which reflects hypophyseal-gonadal relationship, was frequently maintained in the status it had attained before pellet implantation. Excessive bleeding was arrested in several cases in spite of persistence, for instance, of the condition of cystic glandular hyperplasia. It is apparent, therefore, that androgens possess certain pharmacologic properties which permit of its effective use in dosages which do not suppress ovarian activity.

It is true that androgens are frequently employed in conditions in which estrogens may yield equally good or better results. There cannot be any doubt, however, that androgens have a place in the therapeutic armamentarium of many gynecic disturbances. The following instances are a few examples:

1. The menopausal patient a) whose hot flashes are relieved by estrogen therapy but who is disturbed by the accompanying uterine bleeding; the simultaneous administration of small doses of testosterone propionate will prevent uterine bleeding in the greater number of cases, b) in whom estrogens produce marked nervous tension states, uterine bleeding, breast pain, abdominal bloating and pelvic discomfort. Androgens frequently yield gratifying results without undesirable side-reactions.

2. In cases of cyclomastopathy in which estrogen or progesterone fail to alleviate the painful and nodular breasts, testosterone propionate therapy in doses of 10 to 25 mg at weekly intervals for several months frequently yields excellent results. In some of these cases estrogens aggravate the condition. Furthermore, in the suppression of lactation, androgens are superior to estrogens—the former suppress, the latter limit lactation.

3. In cases of dysmenorrhea in which some degree

of endometriosis is suspected or in which small intramural fibromyomas may be present, androgen therapy will yield results whereas estrogen therapy is contraindicated.

4. Androgens may be used for the woman approaching the menopause who has excessive bleeding associated with small fibromyomas or for the woman with large fibromyomas in whom surgery is contraindicated or not feasible

5. The disturbing syndrome of nocturnal frequency of urination when no evident pathologic basis exists for it, may be alleviated by testosterone propionate and the results cannot be matched by estrogen administration.

6. At times, because of acquired frigidity on the part of the female, it may be necessary, if for none other than personal reasons, to restore sexual libido in the hope that dissolution of a marital union may be prevented. Testosterone propionate will restore libido in women who once have known libido but have lost it. In this particular type of case androgens are specific

There are many pharmacologic properties peculiar to testosterone which other steroids do not possess. Gonadal steroids must be thought of not only in terms of sex-spec-

ificity, but also in terms of chemical substances which profoundly influence electrolyte balance, carbohydrate metabolism and nitrogen storage. In this respect testosterone propionate has been shown to be capable of restoring and maintaining a positive nitrogen balance (Albright). The beneficial action to the body economy which may accrue from androgen administration in such patients (with negative nitrogen balance) eliminates the consideration, whether one is dealing with a male or female.

Finally, it should be stressed that clinically effective results are obtainable with dosages of androgens which do not exceed 200 mg. per month, during periods of treatment which are not unduly prolonged without intervals of freedom from therapy. When androgens are so employed, the clinician need not fear the development of arrhenomimetic phenomena. However, I should like to state that I am in complete accord with Doctor Hamblen's emphasis as to the possible irreversible masculinizing symptoms that may result from the injudicious administration of androgens.

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## Abstracts of

# CURRENT CLINICAL LITERATURE

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## ADRENAL

CASHILL, G. F., M. M. MELICOW AND H. H. DARRY

Adrenal cortical tumors. Types of nonhormonal and hormonal tumors. *Surg. Gynec. & Obst.* 74: 281, 1942

Adrenal cortical tumors may occur with or without hormonal syndromes. Of those occurring with hormonal syndromes, changes may be due to excessive formation of androgens or of estrogens or of other steroid substances not yet identified. Symptoms vary according to the type and amount of hormone or hormones produced and by the age and sex of the patient. Adrenal tumors are readily visualized by X-ray after perirenal air insufflation. Removal of adrenal tumors by the transperitoneal route is surgically best. Acute adrenal deficiency occurs only, or mostly, in those with symptoms described as Cushing's syndrome. Therapy is similar to that of acute Addison's disease. Histologically tumors producing hormonal syndromes have cytoplasmic lipid vacuoles in amounts proportional to the symptoms.—D. A. M.

HELLWIG, C. A. AND L. H. FORMAN

Pellagra and internal secretion. *Am. J. Clin. Path.* 12: 210, 1942

Report of a case of pellagra associated with severe endocrine symptoms is presented. The autopsy showed a marked atrophy of the cortex of the adrenal gland with lipid depletion, atrophy of the pituitary, resting thyroid, and hyperplasia of the Langerhans islands of the pancreas. The clinical and anatomical findings suggest a relationship between the pellagra preventing vitamin and the hormones especially the one of the adrenal cortex.—E. von H.

## ENDOCRINE GENERAL

BREA, LUIS MARIA

Hormone therapy in prostatic adenoma. *Rev. sudamer. can. endocrinol.* 24: 495, 1941

Treatment consisted of daily injections of 5 to 10 mg of testosterone propionate for 5 days followed by 5 mg twice weekly. The total amount given was over 50 mg. 19 cases are reported. Frequency of urination was diminished in the majority of the cases, dysuria showed improvement in 50%, retention was improved in six cases. While the adenoma itself did not reveal changes in any case the

general feeling of well being was the most conspicuous consequence of the treatment.—A. E. M.

FRYBERG, R. H.

Treatment of arthritis with vitamin and endocrine preparations. *J. A. M. A.* 119: 1165, 1942

Desiccated thyroid was of limited value in selected cases. Parathyroid and anterior pituitary was of no value. Estrogens were of value in the fibrosis of hypomenorrhea but not in spondylitis rhizomelic. Endocrine preparations are only of value in rheumatic disease when a definite hypofunction of an endocrine gland is present.—C. C. P.

MACDONALD, I.

Mammary carcinoma: a review of 2636 cases. *Surg., Gynec. and Obst.* 74: 75, 1942

A statistical review of clinical records from Cancer Archives of the American College of Surgeons have revealed the following factors. Age of the patient seems not to have any constant prognostic significance although best therapeutic results are obtained in the 35-50 year age group, the least favorable in the sixth decade. A history of familial cancer occurred in 20% of the patients, there being in the cancerous relatives an excess of breast cancer 3 times greater than in the general population. Nulliparae are slightly more prone to develop carcinoma than multiparae, the number of children borne having no relationship to prognosis. A high incidence of failure of lactation in parous women is found in those developing breast carcinoma. 40% of attainable five year cures may be lost by failing to employ radical treatment in Stage II cases. Ten year follow-ups are necessary for true evaluation of therapeutic measures.—Author's summary.

## GONADS

ALBERT, S. AND H. SELYE

The effect of various pharmacological agents on the morphogenetic actions of estradiol. *J. Pharmacol. & Exper. Therap.* 75: 308, 1942

The synergisms and antagonisms of the steroid hormones may help the clinician to accentuate desired therapeutic effects or diminish harmful side effects. Using estradiol in a fixed dose the modifying effect of steroids was studied. They found 1. Androstenediol was most potent in preventing the loss of body weight due to estradiol. 2.



Testosterone and methyl testosterone gave the most clear-cut inhibition of hypophysis hypertrophy. 3. Thy-mus involution is accentuated by all of the steroids. 4. The decrease in testis and kidney weight is prevented only by highly active androgen.—C.C.P.

DANZIGER, L.

Estrogen therapy of agitated depressions associated with the menopause. *Arch. Neurol. and Psychiat.* 47: 305. 1942.

Of 164 cases of probable involuntional melancholia previously reported in the literature and treated with estrogens, 79, or 48%, recovered or improved markedly. Of 29 apparently similar cases treated with placebos, 2, or 7%, recovered or improved markedly. Statistical analysis indicates the results in the two groups are significantly different. Seven new cases treated with diethyl stilbestrol are reported; 4 recovered. Placebos were given before the diethyl stilbestrol without effect.

The absence of a more uniform response to treatment is attributed to heterogeneity of the population studied with respect to psychosis, duration of psychosis, duration of hospitalization before treatment, age, and treatment.—*Author's summary.*

DANZIGER, L. AND H. ROBERT BLANK

Androgen therapy of agitated depressions in the male. *Med. Ann. of the District of Columbia* 9: 181. 1942.

Of 35 cases of probable involuntional melancholia previously reported in the literature and treated with testosterone propionate, 21 recovered or improved markedly and 4 others improved temporarily. Five new cases are reported; two recovered and one showed marked improvement. Placebos given before the testosterone propionate were without effect.

The absence of a more uniform response to treatment is attributed to heterogeneity of the population studied with respect to psychosis.—*Author's summary.*

FREED, S. C., W. M. EISIN AND J. P. GREENHILL

The therapeutic efficiency of diethylstilbestrol esters. *J.A.M.A.* 119: 1412. 1942.

Diethylstilbestrol, diethylstilbestrol dipropionate and diethylstilbestrol dipalmitate were assayed for therapeutic potency in menopausal patients. Judging from the subjective responses diethylstilbestrol dipalmitate was the most active and had fewer undesirable side actions. The dosage used in all cases was equivalent to 5 mg. of the active component diethylstilbestrol.—C.C.P.

HAMILTON, J. B., R. I. DORFMAN AND G. R. HUBERT.

Androgenic and estrogenic substances in urine of eunuchoid and castrated men. Changes following administration of testosterone propionate. *J. Lab. Clin. Med.* 27: 917. 1942.

The average daily androgenic activity of the urine of 7 hypogonadal men was 18.8 I.U. (range 9.0 to 27) and that of 4 castrated men was 7.7 I.U. (range 3 to 11). The average

daily estrogenic activity of the urine of the eunuchoids was 27.4 I.U. (range 8 to 50) and of the castrates 14.7 (range 5 to 28). These titers are lower than those found for normal young men; the range for the androgenic activity is from 22 to 132 I.U. and the range for the estrogenic activity is from 20 to 290 I.U. Daily injection of 20 mg. of testosterone propionate resulted in the elevation of the values for urinary androgenic activity to the range of normal young men. Urinary estrogenic activity was also increased as a result of conversion of testosterone to phenolic estrogenic substances. Upon the withdrawal of the testosterone the values dropped to the previous levels. In terms of molecular conversion to androgens and estrogens, the percentage recovery in the urine of the administered androgen is appreciable and comparable from person to person. Recovery following intramuscular injections in oil is less than that obtained upon implantation of pellets of testosterone propionate but is in turn greater than that occurring after oral administration. The literature pertaining to the biological assay of androgens and estrogens in castrated and eunuchoid men was reviewed and the values obtained by other investigators compared with those obtained in this study. 37 references.—C. P.

LATZ, L. J. AND EMIL REINER.

Further studies on the sterile and fertile periods in women. *Am. J. Obst. and Gynec.* 43: 74. 1942.

Statistical data from approximately 1000 written calendar records of over 11,000 menstrual cycles and approximately 50,000 sterile cohabitations compiled in chart form. This chart provides practical proof that ovulation occurs within a narrow time limit in the cycle, that the period of fertilization of the ovum is very short and that life span of sperm cells inside the female genital tract is not greater than 48 hours. Authors agree to the validity of the biologic law of sterility and fertility as originally propounded by Knaus and support its practicability.—D.A.M.

WALDBOTT, G. L. AND L. J. BAILEY.

Estrogenic hormone determinations in premenstrual asthma. *J. Allergy* 13, 125. 1942.

Blood estrogen content in 56 allergic women who presented a history of premenstrual aggravation of allergy was compared with 23 controls without such a history. In most patients the major diagnosis was bronchial asthma.

Blood used for estrogen assay was obtained between the second and fifth day before menstruation. Of the 56 patients with a history of premenstrual allergy, 35 exhibited negative, 5 a questionably positive, and 16 positive tests for estrogen. Of the 23 allergics without history of premenstrual allergy, 15 showed negative, 1 questionable, and 7 positive tests for estrogen. In a group of 42 non-allergic women with normal menstrual history, negative tests for estrogen were obtained in 2, questionably positive tests in 3, and positive tests in 37.

Thus, in the two groups of 79 allergic patients, 63.3 per cent gave a negative test for estrogen as contrasted with only 4.7 per cent recorded for the non-allergic controls.

Twenty-one unselected women with asthma and vaso motor rhinitis were given large doses (50 000 i.u.) of theelin from one to six times at one to three day intervals irrespective of the date of their menstruation without any effect of the allergic condition. Progesterone therapy was then tried in the same patients and it likewise produced no improvement in the allergic condition.

Another group of 14 patients with perennial asthma vasomotor rhinitis, and definite aggravation of symptoms premenstrually, was studied. Between two and eight doses of theelin and progesterone were given to these women within fourteen days before the expected onset of the menses. Since other therapeutic measures were simultaneously employed, it is difficult to draw conclusions concerning these cases, but it was felt that theelin was helpful at least temporarily in three patients.

Eight patients who had allergic symptoms only before the menses received above injection. Theelin was found to be of value in the control of symptoms in 2 of these patients and progesterone was helpful in 3 others — *Author's summary*

#### WESTBERG, V

Histidinuria: a rapid method for the detection of pregnancy. *Acta Obst et Gynec Scandina* 21 180 1941

Studies were made on specimens of urine of 680 women with intrauterine pregnancy, 11 with extrauterine pregnancy, 61 who had had an abortion, 238 non pregnant women, 19 men with pulmonary tuberculosis and 3 with Cushing's syndrome. The histidine reaction was negative in 6% of women with normal pregnancy and negative in only 3% of women who were in the first 3 months of pregnancy. It was positive for all women with extrauterine pregnancy. The urine of nonpregnant women and of men gave positive reactions in 1.5% of the cases. Serial tests on 14 women in the puerperium showed that the secretion of histidine decreased rapidly after normal delivery. The same seemed true after induced abortion. Comparative mouse, rabbit and histidine tests for pregnancy in 171 cases showed that the histidine test can compete with the two former tests. The author used the method of Kapeller Adler (cf. *Wien klin Wochschr* 47 168, 1934, C A 31 3955) for the detection of histidine — C P

#### WHITACRE, F E, AND L Y FANG

Fatty degeneration of the liver in pregnancy. Report of a case with recovery. Chemical and histologic studies. *J Am Med Assoc* 118 1358 1942

A case of fatty degeneration of the liver in pregnancy is fully described from the point of view of the biopsy findings as well as extensive chemical studies on the blood. The patient recovered. Early termination of pregnancy and immediate continued intravenous administration of glucose as well as liberal transfusions, are essential. It is believed that death results from hypoglycemia rather than from the extent of liver damage — C P

## HYPOPHYSIS

#### BUCHHEIM, F S P VAN

Cushing's disease. *Acta med Scandinavica* 108 544 1941

A patient showing the typical picture of Cushing's disease was observed for 8 years. There was localized osteoporosis of the spine and ribs suggesting a hyperfunctioning parathyroid. At autopsy, a typical basophilic cell adenoma of the hypophysis was found, the other glands being normal. Hyaline changes in the basophilic cells were noted — F R Vanzant, in *Biol Abstracts*

#### SALOMON, HUGO, AND JULIO CESAR LASCANO

An extraordinary case of Simmonds' disease. *Semana med* 49 746 1942

The patient, a man of 40, had a history of an ailment developing during 5 years. It started with nervous disturbances and pain in the joints, later gastrointestinal symptoms prevailed. At the time of first examination a mild anemia, normal glucemia and a good tolerance to 10 units of insulin were observed. Free hydrochloric acid was absent in the gastric juice, the duodenal juice showed traces of trypsin, absence of diastase and considerable reduction of steapsin. Stools were liquid, gray and contained large quantities of fatty acids and soaps. A high calorie diet with 250 to 300 g fat and 20 units of insulin daily kept the weight stationary without improving the symptoms. Cachexia developed gradually concomitantly with a voracious appetite and a B.M.R. of +31. The skin became dry and desquamated in large sheets. The patient developed delirium for a few days but clear consciousness returned preceding death. The pituitary showed diffuse sclerosis and two foci of ischemic necrosis without signs of inflammation. The number of chromophobes was diminished, to a less degree the eosinophils. Sclerosis of the adrenal cortex, atrophy of the thyroid and testes, amyloidosis of the spleen and lymphatic ganglia were considered to be secondary to the pituitary degeneration. The structure of the pancreas was essentially normal — A E M

#### SCHNEIDEWIND, ARTURO AND SIMON TRAJTENBERG

Generalized lentigo in a pituitary dwarf. *Semana med* 48 1535 1941

A boy of 9 years is described whose growth had stopped almost completely when he was 4 years old. A year later there appeared pigmented spots on neck and face, which gradually spread over the thorax, abdomen, back and limbs but not over the mucosae. The face of the patient was characterized by a dry, rough and wrinkled skin. The hair was stringy with little pigment, the skull large and out of proportion with the face. Body size was 1.05 meters. The sella turcica was exceptionally small and the ossification of the bones retarded. The intelligence was normal — A E M

## PANCREAS

HARTZ, P. H.

Routine staining of the beta cells of the islets of Langerhans with Masson's tetrachrome stain. *Arch. Path.* 33: 541. 1942.

The author described a method of routine staining of the beta cells of the islets of Langerhans with Masson's tetrachrome stain. Fixation of the material in a mixture of equal parts of Bouin's fluid and a saturated aqueous solution of mercury bichloride was suggested. The tissues were imbedded in paraffin and sections 6 microns thick were prepared with the microtome. After removal of the mercury precipitate the sections were stained by the method of Larson and Levin (*Arch. Path.* 29: 272, 1940), the only difference being that fast green F. C. F. was substituted for light green. Beta cells appeared closely packed with red-staining granules and contrasted sharply with the other island cells, which showed a pale brownish color.—E. von H.

WOLF, WILLIAM.

Sensitivity to protamine zinc insulin. *Arch. Dermat. & Syph.* 45: 694. 1942.

A case of allergic reaction consisting in an itching eruption of the arms, dorsa of the hands and palms was reported following the administration of protamine zinc insulin. The diagnosis was confirmed by the intracutaneous injection of protamine zinc insulin, which produced a decided reaction within 3 minutes. Since neither protamine nor zinc are antigens, and since the true sensitivity to unmodified insulin is rare, the author explained the occurrence of this sensitization to insulin as a result of its delayed absorption due to the presence of protamine and zinc.—E. von H.

## THYROID

CANTILLO, ENRIQUE, AND CARLOS FERNANDEZ SPERONI.

Endocrinopathies VII. Filbrilloflutter in a severe thyrotoxicosis. *Semana méd.* 49: 755. 1942.

A woman of 37 years originating from a region where goiter is endemic and having a history of mild goiter developed severe cardiac symptoms of the following characteristics: apnea, auricular fibrillation, ventricular extrasystoles, dilatation of the cardiac area, pulmonary congestion. The electrocardiogram showed complex QRS waves with high voltage, flat T wave, complete arrhythmia. Arterial pressure 120/75. Orthostatic pulse 140. There was no loss in weight, the eyes were rather retracted in the orbits. It is pointed out that hyperthyroidism at the age of approaching menopause with a history of goiter is usually not of the Grave's disease type. The B.M.R. was +27 and 30, cholesterol 200 mg. The increase in blood sugar after 100 g of glucose was 122 mg. After thyroidectomy the pulse rate dropped to 75 and the arrhythmia disappeared. The E.K.G. became normal.—A. E. M.

COHN, A., AND S. E. FELDMAN.

The relation between the liver and the thyroid gland. I. Blood iodine as an indicator of liver function. *Am. J. Clin. Path.* 12: 27. 1942.

The influence of liver and gallbladder diseases on the blood iodine level was investigated. Iodine analyses were made by the method of Trevorrow and Fashena. Liver damage was produced experimentally in rabbits with carbon tetrachloride inhalations. It was found that liver and gallbladder disease did not elevate the blood iodine and that the functional relationship between liver and thyroid could not be expressed by the blood iodine level.—E. von H.

MARINE, DAVID, AND SAMUEL H. ROSEN.

Urinary excretion of capon comb growth-promoting substances in Graves' disease and myxedema and modification following iodine and desiccated thyroid therapy. *J. Mt. Sinai Hosp.* 8: 811. 1942.

Androgenic substances extracted from the urine by the method of Dingemans, et al. were determined by the Fussgänger modification of the capon comb test. Administration of large amounts of iodine usually depressed the urinary androgen excretion in true Graves' disease, particularly if there was other evidence of clinical improvement, but not in non-Graves' patients. Desiccated thyroid administration to the point of elevating the basal metabolic rate did not definitely lower the amount of androgen excreted in non-myxedema patients but caused a significant rise in the 2 cases of myxedema of adults studied. In Graves' disease the absolute amount of androgen excreted in the urine varied widely; in some cases it was normal but more often was reduced. If the amount of androgen excreted is significant, it can only be a relative increase creating an imbalance in the realm of the steroid hormones. Possibly, one of the causes for improvement of patients with Graves' disease after partial thyroidectomy is that it aids in correcting such an imbalance. In myxedema of adults there appears to be an absolute decrease in the urinary excretion of androgen which may be raised by treatment with desiccated thyroid—Ruth Berggren, in *Chem. Abstracts*.

SILVER, SOLOMON, AND BORIS MAGASANIK.

The blood iodine in the period after thyroidectomy. Preliminary report. *J. Mt. Sinai Hosp.* 8: 1027. 1942.

Blood iodine (nondialyzable fraction) was elevated in all 7 cases of Graves' disease studied. Treatment with iodine tended to lower the blood iodine coincident with clinical improvement. The blood iodine underwent an average increase of 1.9  $\mu\text{g}\%$  immediately after thyroidectomy and returned to preoperative levels in 24 hrs. after completion of the operation in most cases. The 2 patients with the highest blood iodine values in the postoperative period were the same 2 who had the most unfavorable postoperative course.—Ruth Berggren, in *Chem. Abstracts*.

# The Journal of CLINICAL ENDOCRINOLOGY

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## Comparative Study of Metabolic Effects of Estradiol Benzoate and Testosterone Propionate in Man<sup>1,2,3</sup>

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IN EXTENDING the work of Thorn and Harrop (1) describing the sodium retaining influence of several steroids of the sex hormone series Thorn and Engel (2) noted that the urinary excretion of nitrogen and inorganic phosphorus was depressed by estradiol, estrone or pregnancy urine estrogens. Thus, 5 mg of estradiol benzoate given in one injection to a normal male dog reduced urinary nitrogen from 10.4 to 8.2 gm the second day after injection and reduced urinary inorganic phosphorus from 0.56 gm per day to 0.43 and 0.39 gm on the second and third days after injection. Urinary sodium and chloride also declined as in the earlier experiments while urinary potassium was unaltered. Evidence was further provided that these effects were not mediated by the adrenal cortex. In adrenalectomized dogs pregnancy

urine estrogens partially retarded the diuresis of sodium and chloride, consequent upon withdrawal of adrenal extract. Seventeen mg of estradiol benzoate given in a single injection to a woman with Addison's disease from whom adrenal extract was withdrawn reduced urinary nitrogen, inorganic phosphorus, sodium and chloride excretion.

From this it would appear that the properties of several androgens in inducing retention of nitrogen and inorganic phosphorus in dogs and man (2-6) may be shared, to some extent at least, by estrogens. Subsequent work, however, has both elaborated and complicated our knowledge of the metabolic properties of estrogens in man. Albright, Bloomberg and Smith (7) examined the effects of estradiol benzoate in women with postmenopausal osteoporosis. As a rule they injected 1.66 mg intramuscularly every second or third day. In the 3 subjects studied a striking retention of calcium, reaching a maximum of 0.8 to 1.0 gm per 5-day period and of phosphorus, reaching 0.4 to 0.7 gm per 5-day period occurred. Estradiol was conceived as repairing defective bone matrix and permitting in consequence the deposit of bone salts. No modification of the rate of bone resorption was

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<sup>2</sup> T. H. R. Robinson.

date used  
Dr. Max

An abstract of this paper was read at the 35th Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics, April 4, 1942.

postulated. In contrast to the experience of Thorn and Engel, no distinct evidence of nitrogen retention was obtained in the two subjects studied. In two osteoporotic subjects with Cushing's syndrome, Albright, Parson and Bloomberg (8) found that no retention of calcium, phosphorus or nitrogen was induced by estradiol benzoate, although testosterone propionate, 25 mg. daily, effected conspicuous retention of all 3 substances. The osteoporosis in Cushing's syndrome is conceived by these authors as arising

seen by Thorn or Albright and their coworkers could be demonstrated.

From the foregoing, it is clear enough that much more information is needed concerning the metabolic effects of the estrogens in man under a variety of endocrinologic conditions.

In the present account we will describe certain of the metabolic effects of estradiol benzoate when given in 5-mg. (30,000 rat units) amounts daily intramuscularly to 2 eunuchoids, 2 women with ovarian insuf-

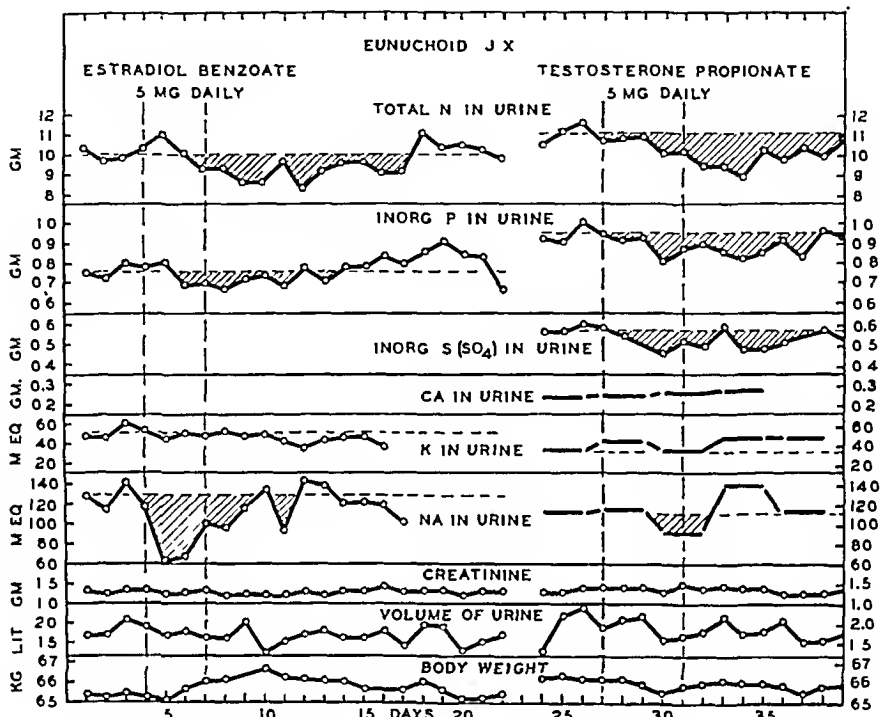


Fig. 1, a and 1, b. EFFECTS OF ESTRADIOL BENZOATE AND TESTOSTERONE PROPIONATE given intramuscularly on the excretion of several urinary constituents and on the body weight of the eunuchoid J. X. The two experiments were not performed consecutively. Interrupted lines designate pretreatment baselines. Shaded areas indicate those changes in values interpreted as significant. Sulfate was determined and is expressed in terms of S.

from dissolution of protein matrix under the influence of adrenal cortical hormones. Testosterone propionate was held to repair this matrix, estradiol benzoate not. The variations in calcium metabolism were believed to be secondary to variations in the amounts of calcifiable matrix.

In 5 normal girls, 9 to 13 years old, Johnston (9) observed no evidence of either nitrogen or calcium retention during treatment with theelin given in amounts of 2000 units (rat units or international units?) daily for 6 to 18 days. Indeed, an increase in both urinary and fecal calcium excretion occurred, together with some irregular nitrogen loss. Diethylstilbestrol had a similar effect in another girl. Thus, by virtue either of the types of estrogen used, of the dosage or of the normalcy of the subjects, none of the metabolic effects on nitrogen or calcium metabolism

efficiency, one of whom was masculinized, and one normal woman. In the 2 eunuchoids these effects will be compared with those resulting from 5 mg. daily of testosterone propionate. Supplementary data on the responses of the eunuchoid and the hypogonad woman to larger doses of testosterone propionate are included.

It must be kept in mind that while the smaller amounts of testosterone propionate used (5 mg. daily) fall below replacement requirements, the same amounts of estradiol benzoate substantially exceed such requirements. While such high dosage is useful in dramatizing response in orientation experiments, and is necessary for detailed comparison with the physiologically weaker androgens, application of the data so obtained to the problems of normal ovarian physiology must be made with due reservation.

## METHODS

The subjects were given weighed diets containing the same food each day, of sufficient caloric content to permit maintenance of weight, with activity in accordance with the particular individual's desires and capacity. The metabolic and chemical methods used were for the most part described or cited previously (5). Added chemical determinations were inorganic sulfate in urine by the method of Koch (10), total nitrogen in weighed amounts of dried food and feces by the Kjeldahl method as used by us for urine total nitrogen, total phosphorus in food and feces by application of the method for inorganic phosphorus of Fiske and Subbarow (11) to the further diluted ash solution prepared for calcium determinations as below, and calcium in food, feces and urine by the following technique. Appropriate amounts of the dried material were ashed in the muffle furnace at  $500-550^{\circ}\text{C}$ , the ash was extracted with 10 per cent hot hydrochloric acid and the extract made to such volume that 1 to 3 cc contained 0.1 to 0.3 mg of calcium. After adjustment of the pH of such samples to 4.2 to 4.4 with ammonium hydroxide using 0.1 per cent bromocresol green as indicator, the calcium content was determined by the technique developed for serum by Kramer and Tisdall, and modified by Clark and Collip (12). The photoelectric colorimeter was used for measurement of the color produced in the determination of creatine and creatinine by the Jaffe alkaline picrate reaction.

In preparation of food for analysis, 50 per cent aliquots of each day's diet were collected in porcelain evaporating dishes for the periods given. The sample for each period was mixed and dried to constant weight at  $60$  to  $65^{\circ}\text{C}$ , and the residue was then ground and mixed. Feces were collected in glass jars, the respective periods defined by carmine markers. The feces for each period were diluted and thoroughly mixed with an approximately equal weight of water, acidified to bromophenol blue with 10 per cent hydrochloric acid in ethyl alcohol, then dried to constant weight at  $60$  to  $65^{\circ}\text{C}$ . The residue was ground in a mortar until it could be passed through a 20 mesh sieve.

## PROTOCOLS

*JX* (referred by Dr Carl Moore) was a 28 year old eunuchoid described in detail previously (5) when an account of his response to 25 and 50 mg of testosterone propionate daily was given. The experiments described in figures 1, b and 2 were performed in October and December of 1939. He received a diet of C 282, P 68, F 162, Calories 2858, estimated to contain 10.9 gm of N, 0.887 gm of S, 1.295 gm of P, 0.808 gm of Ca, 1.099 gm of Na, 1.387 gm of Cl and 2.767 gm of K. To this 4 gm of NaCl was added at the table. The experiment described in figure 1, a was performed in January, 1940. He received

a diet of C 294, P 72, F 162, Calories 2922, estimated to contain 11.5 gm of N, 0.783 gm of S, 1.265 gm of P, 0.806 gm of Ca, 1.198 gm of Na, 1.543 gm of Cl and 2.868 gm of K. To this 4 gm of NaCl was added at the table. The fluid intake, including distilled drinking water, was 2450 cc daily throughout all experiments. Before treatment basal metabolic rates of -25 and -27, with

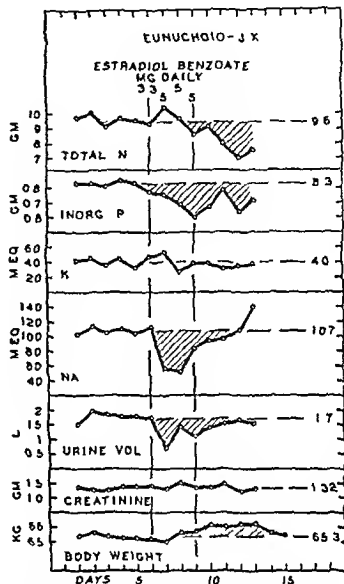


Fig 2 EFFECTS OF ESTRADIOL BENZOATE GIVEN INTRAMUSCULARLY ON METABOLIC CONSTITUENTS AND ON THE BODY WEIGHT OF EUNUCHOID JX. Interrupted lines and the corresponding pretreatment baselines. Shaded areas indicate changes in values interpreted as significant.

basal total Calories for 24 hours of 1315 and 1272 were obtained in December.

*JD* (referred by Dr I Becker, University of Illinois) was a 34-year old eunuchoid studied from September to December, 1941. He was 182 cm (72 8 in) tall and weighed 76 kg. (167 2 lb) at the outset. The span was 183 cm, the sitting height 92.1 cm. The face was smooth, the small amount of facial fuzz being shaved every 2 or 3 weeks, pubic hair was scant, axillary hair somewhat more abundant. Lumb and trunk hair was scant. The skin of the trunk and limbs was disfigured by an extensive congenital ichthyosis. The voice was somewhat above average masculine pitch and the laryngeal prominence was not well felt. A considerable prominence of the breast regions was judged after biopsy to be largely adipose tissue without glandular components. The well formed penis was 1.5 cm long and 7.5 cm thick at the corona. The small well differentiated scrotum was usually empty but at times two

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE ON THE NITROGEN, PHOSPHORUS AND CALCIUM BALANCES AND ON THE CONCENTRATION OF SEVERAL BLOOD CONSTITUENTS OF THE EUNUCHOID N.D.

| Day            | Total N, gm./day |               |       | Total P, gm./day |               |                | Ca, gm./day |               |       | Plasma      |           | Serum |          | Body Wt. kg. |
|----------------|------------------|---------------|-------|------------------|---------------|----------------|-------------|---------------|-------|-------------|-----------|-------|----------|--------------|
|                | Food             | Feces         | Urine | Food             | Feces         | Urine (inorg.) | Food        | Feces         | Urine | Prot. gm./% | NPN mg. % | P     | Ca mg. % |              |
| 1              | 11.88            | 1.32<br>+0.42 | 10.14 | 0.99             | 0.40<br>-0.04 | 0.63           | 0.35        | 0.37<br>-0.12 | 0.09  | 7.12        | 27        | 4.3   | 9.9      | 59.6         |
| 2              |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 59.6         |
| 3              |                  |               |       |                  |               |                |             |               |       | 7.31        | 25        | 4.3   | 9.3      | 59.8         |
| 4              |                  |               |       |                  |               |                |             |               |       |             |           |       |          |              |
| 5 <sup>1</sup> | 11.88            | 1.25<br>+3.50 | 7.13  | 0.99             | 0.37<br>+0.21 | 0.41           | 0.35        | 0.38<br>-0.09 | 0.07  | 6.91        | 20        | 3.8   | 9.7      | 59.8         |
| 6              |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 59.7         |
| 7              |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 59.6         |
| 8              |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 59.8         |
| 9              |                  |               |       |                  |               |                |             |               |       | 6.84        | 20        | 3.5   | 9.1      | 60.1         |
| 10             |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 60.2         |
| 11             |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 60.2         |
| 12             |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 60.6         |
| 13             | 11.88            | 1.24<br>+2.43 | 8.21  | 0.99             | 0.37<br>-0.02 | 0.64           | 0.35        | 0.38<br>-0.09 | 0.06  | 6.79        | 17        | 3.4   | 8.9      | 61.0         |
| 14             |                  |               |       |                  |               |                |             |               |       | 6.56        | 17        | 3.6   | 9.4      | 61.3         |
| 15             |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 61.6         |
| 16             |                  |               |       |                  |               |                |             |               |       |             |           |       |          |              |
| 17             |                  |               |       |                  |               |                |             |               |       | 6.83        | 18        | 4.3   | 9.3      | 61.5         |
| 18             |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 61.3         |
| 19             |                  |               |       |                  |               |                |             |               |       |             |           |       |          |              |
| 20             |                  |               |       |                  |               |                |             |               |       | 7.19        | 21        | 4.3   | 9.3      | 60.6         |
| 21             |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 60.8         |
| 22             |                  |               |       |                  |               |                |             |               |       |             |           |       |          | 60.8         |

<sup>1</sup> Testosterone propionate, 25 mg. daily intramuscularly, was given from day 5 to day 12 inclusive. Estimated balances are in boldface type.

very small bodies, sensitive to pressure could be felt. The prostate was not palpable.

Röntgenograms of the skull showed a somewhat shallow, but otherwise normal, sella turcica. The fundi and visual fields were normal. Epiphyses of the shoulder girdle, elbow, and hand were all fused with their respective diaphyses. Those of the iliac crests were, however, still unfused, this delay of some 14 years constituting the only

TABLE 2. EFFECT OF ESTRADIOL BENZOATE ON THE CONCENTRATION OF BLOOD-UREA NITROGEN, SERUM INORGANIC PHOSPHORUS AND HEMATOCRIT OF THE EUNUCHOID J.D.

| Day <sup>1</sup> | Blood Urea N, mg. % | Serum Inorganic P, mg. % | Hematocrit, vol./100 cc. |
|------------------|---------------------|--------------------------|--------------------------|
| x                | 10.8                | 4.1                      | 41                       |
| y                | 10.3                | 4.7                      | 44                       |
| 5 <sup>2</sup>   | 12.0                | 4.2                      | 43                       |
| 7                | 10.6                | 3.9                      | 43                       |
| 9                | 8.1                 | 3.9                      | 41                       |
| 12               | 8.3                 | 3.9                      | 41                       |
| 14               | 9.4                 | 4.3                      | 42                       |
| 19               | 9.3                 | 3.8                      | 43                       |
| 21               | 10.7                | 4.2                      | 42                       |
| 25 <sup>3</sup>  | 10.1                | 4.1                      | 40                       |
| 28               | 7.7                 | 4.1                      | 39                       |
| 34               | 8.8                 | 4.3                      | 42                       |

<sup>1</sup> Days x and y control days preceding enumeration as given in figure 3.

<sup>2</sup> Estradiol benzoate intramuscularly 5 mg. daily days 5 to 9 inclusive.

<sup>3</sup> Testosterone propionate intramuscularly 5 mg. daily days 25 to 34 inclusive.

evidence of retarded epiphyseal fusion. An oral glucose tolerance test showed a flat curve, the blood-sugar values ranging from 72 to 88 mg. per cent, but an intravenous glucose tolerance test was normal. An intravenous insulin tolerance test (0.1 u of insulin/kg. = 7.6 u of insulin) produced hypoglycemia (29 mg.%) at .5 hour with symptoms, but the return to approximately baseline values at 2 hours (80 mg.%) was normal.

Assays for 17-ketosteroids, colorimetric as by Holtorf and Koch,<sup>4</sup> gave a value of 18.1 mg. per day for a 6-day collection. By capon-comb assay only 1 to 3 international units per day could be detected. Thus, although a normal amount of color-yielding material was present, only a small fraction of this was androgenic. The precise amount of urinary gonadotropins (mouse uterine method) was not determined although Dr. Varney found more than 30 mouse units excreted per day. Thus, normal amounts at least were present and no evidence accordingly is adduced that the hypogonadism was primarily of pituitary origin.

In conclusion J.D. was a eunuchoid suffering presumably from primary testicular insufficiency of unknown origin.

The data shown in figure 3 and table 2 were acquired while the subject was on a constant diet of C 306, P 85, F 136, Calories 2788. This was estimated to contain 1.080 gm. of S, 1.196 gm. of Na, 1.756 gm. of Cl and 4.552 gm. of K. By analysis it contained 14.6 gm. of N, 1.29 gm. of P, and 0.77 gm. of Ca per day. To this, 4 gm. of

<sup>4</sup> The assays for 17-ketosteroids were made by Mr. Paul Munson and Mr. Carter Johnston in the Department of Biochemistry.

NaCl was added at the table. Fluid intake, including distilled drinking water, was kept constant at 2800 cc. per day. Creatine, 1.32 gm., was ingested daily at breakfast beginning 4 days before treatment with estradiol benzoate.

The data shown in figure 4 and table 3 were acquired while the subject was on a diet of C 296, P 86, F 122, Calories 2626. This was estimated to contain 1.027 gm. of S, 1.091 gm. of Na, and 3.516 gm. of K. By analysis it

N.D. was a 34-year-old eunuchoid, in whom both the clinical features and metabolic response to testosterone propionate, 25 mg. daily, have been described (4). He was re-studied in February, 1940, having been untreated for 9 months. The metabolic data are given in table 1. At this time his diet comprised C 269, P 64, F 107, Calories 2295. By analysis this provided 11.88 gm. of N, 0.99 gm. of P and 0.351 gm. of Ca. Four gm. of sodium chloride

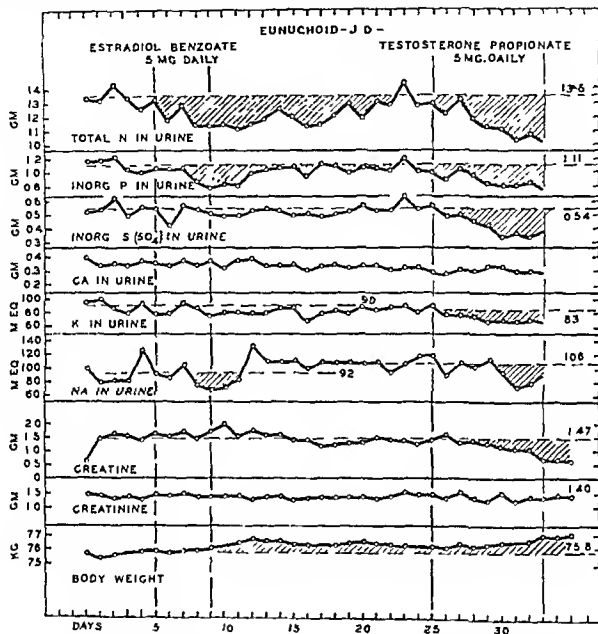


Fig. 3. EFFECTS OF ESTRADIOL BENZOATE AND TESTOSTERONE PROPIONATE, given intra-

contained 15.2 to 15.4 gm. of N, 1.28 to 1.36 gm. of P, and 0.73 to 0.77 gm. of Ca. Four gm. of NaCl was added daily at the table. Fluid intake, including distilled drinking water, was kept at 2500 cc. daily. Creatine, 1.32 gm., was ingested daily throughout the experiment.

The data given in figure 3 do not include values for basal heat production during the experiments with 5 mg. of estradiol benzoate and 5 mg. of testosterone propionate daily. The range was from -14 to -21, 1464 to 1595 Calories per 24 hours without any variation attributable to the treatment used. After the conclusion of the period of treatment with 5 mg. of testosterone daily shown in figure 3, 25 mg. of testosterone propionate was given daily for 5 days without further effect on the creatinuria. Thirteen days after discontinuing the androgen the experiment shown in figure 4 and table 3 was begun

was added at the table and a constant fluid intake, including distilled drinking water, and amounting to 2250 cc. daily was provided. The basal metabolic rates before treatment were -18 and -19 and 1329 and 1311 total Calories per 24 hours.

A.B. (referred by Dr. Sara Janson) was an 18-year-old girl who was short (147 cm., 4 ft. 9.5 in.) and had scant pubic and axillary hair, flat breasts, juvenile genitalia and primary amenorrhea. The urinary gonadotropins were 250 and 400 to 450 mouse units per day, values equal to those of the castrated or menopausal woman. She has been fully described as a member of an interesting group of hypogonadal women (13). The metabolic studies were made in April and May of 1940 and are illustrated in figure 5 and table 4. At this time she ate a diet of C 218, P 42, F 85, Calories 1805, estimated to contain 6.72 gm.



TABLE 3. EFFECT OF ESTRADIOL BENZOATE ON THE NITROGEN, PHOSPHORUS AND CALCIUM BALANCES AND ON THE CONCENTRATION OF SEVERAL BLOOD CONSTITUENTS OF THE EUNUCHOID J.D.

| Days                 | Total N, gm./day |               |       | Total P, gm./day |               |                | Calcium, gm./day |               |       | Blood           | Plasma         |              | Serum      |             |             | Hemato-<br>crit,<br>vol./100 cc. |
|----------------------|------------------|---------------|-------|------------------|---------------|----------------|------------------|---------------|-------|-----------------|----------------|--------------|------------|-------------|-------------|----------------------------------|
|                      | Food             | Feces         | Urine | Food             | Feces         | Urine (inorg.) | Food             | Feces         | Urine | Urea N<br>mg. % | Prot.<br>gm. % | NPN<br>mg. % | P<br>mg. % | Ca<br>mg. % | Na<br>mm/l. |                                  |
| 3<br>4<br>5<br>6     | 15.40            | 1.85<br>-0.24 | 13.79 | 1.35             | 0.30<br>+0.03 | 1.02           | 0.77             | 0.40<br>+0.13 | 0.23  | 13.4            | 7.42           | 21           | 4.2        | 9.7         | 145         | 44                               |
| 7<br>8<br>9<br>10    | 15.24            | 1.84<br>+0.32 | 13.08 | 1.28             | 0.33<br>-0.02 | 0.97           | 0.73             | 0.43<br>+0.10 | 0.20  | 9.9             | 7.27           | 21           | 3.7        | 9.5         | 144         | 45<br>45                         |
| 11<br>12<br>13<br>14 | 15.78            | 1.68<br>+1.76 | 12.34 | 1.36             | 0.29<br>+0.22 | 0.86           | 0.73             | 0.37<br>+0.13 | 0.24  | 9.2             | 6.89           | 17           | 3.9        | 9.2         |             | 43                               |

<sup>1</sup> Estradiol benzoate, 5 mg. daily intramuscularly, from day 7 on.  
Balances in boldface type.

of N, 0.597 gm. of S, 0.810 gm. of P, 0.617 gm. of Na, 0.916 gm. of Cl, and 2.152 gm. of K. Four gm. of NaCl was added daily at the table. The fluid intake, including distilled drinking water, was kept constant at 1920 cc. daily. Basal metabolic rates before treatment ranged from -10 to -14, and from 1020 to 968 total Calories per 24 hours.

R.F. (referred by Dr. I. Becker) was a 26-year-old woman who was short (141 cm., 4 ft. 7 in.) and had scant pubic and axillary hair, hypoplastic breasts and genitalia and primary amenorrhea. The urinary gonadotropins, like those of A.B., were high, ranging between 250 to 350 mouse units per day. She likewise has been fully described (13). The metabolic studies reported here were performed in November, 1940, and are illustrated in figure 6. At this time she ate a diet of C 263, P 56, F 92, Calories 2104, estimated to contain 8.96 gm. of N, 0.70 gm. of S, 0.93 gm. of P, 0.87 gm. of Na, 0.91 gm. of Cl, and 2.74 gm. of K. Five grams of NaCl was added at the table. Fluid intake, including distilled drinking water, was kept constant at 2200 cc. daily. The basal metabolic rate, after training ranged from -6 to -8, the basal total Calories per 24 hours, from 1025 to 1053.

TABLE 4. BLOOD CONSTITUENTS OF A.B. DURING TREATMENT WITH ESTRADIOL BENZOATE

| Day             | Blood<br>Urea N<br>mg./100 cc. | Serum<br>Inorg. P<br>mg./100 cc. | Serum<br>Na<br>m.m./l. | Serum<br>K<br>m.m./l. | Hematocrit<br>vol. % |
|-----------------|--------------------------------|----------------------------------|------------------------|-----------------------|----------------------|
| 6 <sup>1</sup>  | 7.3                            | 4.4                              | 135.7                  | 4.56                  | 42                   |
| 7               | 8.1                            | 4.5                              | 137.6                  | 4.50                  | 42                   |
| 9               | 10.0                           | 4.9                              | 136.6                  | 4.48                  | 42                   |
| 10              | 8.7                            | 4.6                              | 137.2                  | 4.50                  | 39                   |
| 14              | 9.5                            | 4.7                              | 139.1                  | 4.76                  | 41                   |
| 17 <sup>2</sup> | 7.3                            | 4.0                              | 133.8                  | 4.70                  | 40                   |
| 21              | 5.2                            | 3.7                              | 142.5                  | 4.66                  | 39                   |
| 23              | 5.5                            | 3.9                              | 142.8                  | 4.78                  | 41 (day 24)          |
| 27              | 5.8                            | 4.0                              | 140.8                  | 4.57                  | 41 (day 28)          |
| 30              | 7.1                            | 4.1                              | 138.1                  | 4.61                  | 41                   |
| 35              | 7.5                            | 4.5                              | 139.4                  | 4.61                  | 42 (day 36)          |

<sup>1</sup> Progesterone 15 mg. daily, days 6, 7, 8 and 23, 24, 25.  
<sup>2</sup> Estradiol benzoate, 5 mg. daily, days 15-25 inclusive.

V.F. was a 20-year-old masculinized girl with ovarian insufficient. She was short (144 cm., 4 ft. 8 in.) with a relatively long trunk (81 cm. sitting height). The span (143 cm.) bore the usual relation to stature. The patient's musculature was sturdy, her manner direct, with a suggestion of masculinity. Her tastes were feminine. Little or no sexual desire was recognized. She had never menstruated. The body hair was abundant and of masculine

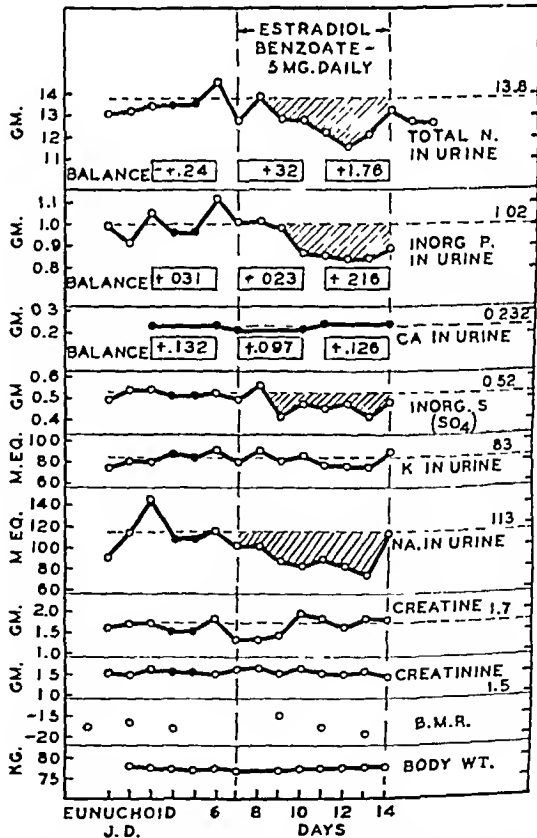


Fig. 4. EFFECTS OF ESTRADIOL BENZOATE given intramuscularly on the excretion of several urinary constituents and on the basal metabolic rate and body weight of the eunuchoid J.D. Interrupted lines and the corresponding figures on the right designate pre-treatment baselines. Shaded areas indicate changes in values interpreted as significant. Blocks summarize the balances detailed in table 3. Sulfate was determined and is expressed in terms of S. Creatine hydrate, 1.32 gm. daily by mouth.

distribution with a moderate excess of unpigmented slightly coarse hair on the face. The voice was deep. Mammary areas bore small nipples and no palpable breast tissue. The clitoris was 2 cm long with a well defined glans and no prepuce. The labia majora were not prominent and contained no gonadal inclusions. The urethra opened into the vulva. Beneath the urethra was a narrow vaginal opening admitting a little finger. A cord like structure occupied the uterine position on rectal examination. No prostatic tissue could be felt. Neither gonad could be palpated. Seven years previously Dr T G Amos of Detroit had explored the abdomen. Small ovaries

obtained less than 10 mouse utrine units of gonadotropic material per day in a 3 day collection.

The data shown in figure 7 were obtained in June and July, 1941. She consumed at this time a diet of C 235, P 54, F 82, Calories 1894, containing an estimated 8.64 gm of N, 0.65 gm of S, 1.16 gm of P, 1.10 gm of Ca, 0.976 gm of Na, 1.53 gm of Cl and 3.08 gm of K. She received, in addition, 4 gm of NaCl added at the table. Because of the warmth of the weather variation was allowed in the amounts of distilled drinking water, the total fluid intake varying accordingly from 1650 to 2600 cc. It was constant at 1900 cc from day 1 through day 10.

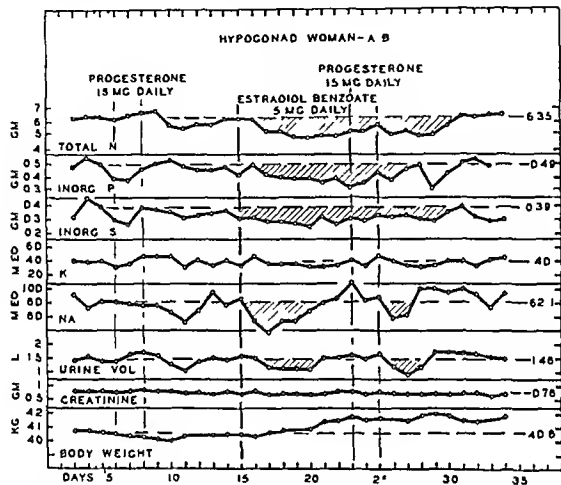


Fig 5 THE EFFECTS OF ESTRADIOL BENZOATE given intramuscularly on several urinary constituents and body weight of the short hypogonad girl A B. Interrupted lines and the corresponding figures on the right designate pre treatment baselines. Shaded areas indicate changes in values interpreted as significant. Sulphate was determined and is expressed in terms of 5

and uterus were found in the normal position. No tumor masses were found in either adrenal. Biopsy specimens of each ovary showed numerous follicles largely undeveloped. Since pyelograms gave no evidence of kidney displacement at the present time the abdomen was not again opened.

The sella turcica was normal on roentgen ray examination. The epiphyseal cartilages of the hand, shoulder, knee and pelvis were all ossified, indeed roentgenograms of the elbow and knee at 13 years of age showed fusion of epiphyses (Dr Amos). The pelvis was interpreted as generally contracted.

Colormetric measurements of urinary 17 ketosteroids<sup>1</sup> gave a value of 61 omg per day (5-day sample). By capon assay, 54 i.u. of androgenic activity were excreted per day. One year previously a 6 day collection had shown 122 mg per day with a very high androgen assay (capon's comb) of 385 i.u. per day. The equivalent of 5 micrograms of estrone was present in both specimens. Dr Varney

(fig 7) and at 2100 cc from day 15 to the end. The basal heat production ranged from  $\pm 0$  to  $+1$  and from 1193 to 1202 total Calories per 24 hours before treatment.

The concentration of several blood constituents was unaltered by treatment with estradiol benzoate. These may be noted as follows: plasma proteins 6.20 to 7.01 gm per 100 cc, plasma non protein N 19 to 22 mg per 100 cc, serum Ca 8.9 to 9.4 mg per 100 cc, P 4.1 to 4.4 mg per 100 cc, Na 134.2 to 142.1 m eq per liter, Cl 98.4 to 102.6 m eq per liter and K 4.18 to 4.59 m eq per liter.

The estradiol benzoate had no effect on breast buds and produced no bleeding from the uterus on withdrawal of treatment. She later developed breast tissue during treatment with diethylstilbestrol while under the care of Dr M E Davis.

B S was a normal 19 year old girl with regular menses occurring every 25 to 27 days and lasting 3 days. Pain

was present on occasion during the first day. The experiment illustrated in figure 8 was performed in April and May, 1941. Estradiol benzoate was started on the 16th day of the menstrual cycle. She menstruated normally the 3rd day after stopping treatment, providing an interval of normal length. The diet comprised C 280, P 59, F 95, Calories 2211; and was estimated to contain 9.44 gm. of N, .075 gm. of S, 1.13 gm. of P, 1.04 gm. of Na, 1.44 gm. of Cl and 2.80 gm. of K. To this 4 gm. of NaCl was added at the table. The fluid intake, including distilled drinking

decline of 6.40 gm. per day with 25 mg. of testosterone propionate daily. Since 50 mg. of testosterone propionate had no more effect than 25 mg. nearly half of the possible androgen influence on nitrogen metabolism was obtained with the small dose of 5 mg. daily. J.X. (fig. 1, b) further illustrates the same point. At the time of maximum effect of 5 mg. of testosterone propionate, a decline in urinary nitrogen of 1.8 gm. per day occurred. In a previous experiment

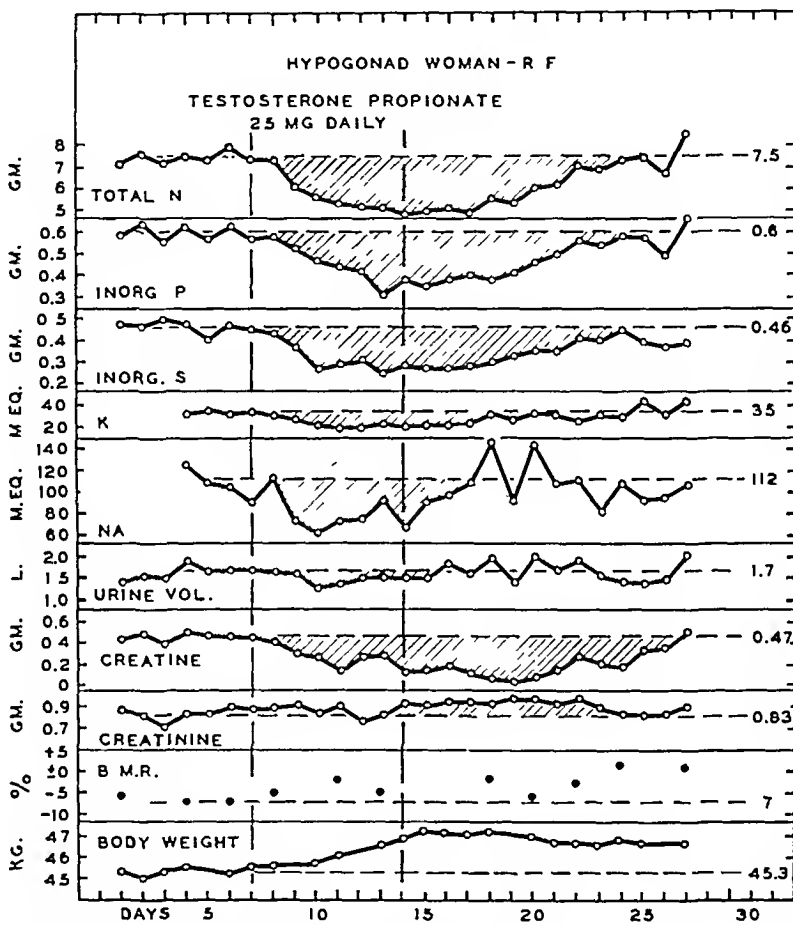


Fig. 6. EFFECTS OF TESTOSTERONE PROPIONATE given intramuscularly on several urinary constituents, basal metabolic rate and body weight of the short hypogonad girl R. F. Interrupted lines and the corresponding figures on the right designate pre-treatment baselines. Shaded areas indicate changes in values interpreted as significant. Sulphate was determined and expressed as S.

water, was kept constant at 2000 cc. daily. The basal metabolic rate ranged from -5 to -9 and from 1307 to 1255 total Calories per 24 hours.

DISCUSSION

Many of the characteristic metabolic effects of testosterone propionate may be obtained in the eunuchoid with as little as 5 mg. daily intramuscularly. Thus in J.K. (cited by Sandiford, Knowlton and Kenyon, 14, fig. 2) a decline in urinary nitrogen of 3.04 gm. per day at the time of maximum influence, occurred with 5 mg. of the androgen as compared to a

(4) 25 mg. produced a decline of 3.3 gm. per day in this subject. A similar distinct reduction in urinary nitrogen of at least 3.0 gm. per day is shown in the eunuchoid J. D. (fig. 3) with the small dose. Urinary inorganic phosphorus was reduced by 5 mg. of testosterone daily in both J. X. and J. D., as was urinary sodium. Urinary potassium was reduced in J. D. and was unaffected in J. X. Urinary inorganic sulfate was decisively reduced in both. No change was produced in the urinary calcium of either subject. This last was to be expected since neither urinary nor fecal calcium excretion was affected in an experiment of this dura-

tion in the eunuchoid *N D* who received 25 mg of testosterone propionate daily (table 1). The creatinuria induced in *J D* by oral administration of creatine was reduced materially by 5 mg of testosterone propionate daily. It is of passing interest that this creatinuria was not further modified by the subsequent administration of 25 mg of testosterone propionate daily. The elevation of basal heat production in *J D* during this experiment was insignificant, but we have already pointed out that even with heavier dosage considerable time may often elapse before notable increase in heat production occurs (14).

The sensitivity of the eunuchoid to the metabolic

small amounts of androgens necessary to initiate metabolic response seem to fall below those required for conspicuous evolution of most secondary sex characters, the testicular contribution to adolescent growth may begin relatively early, before secondary sex characters are well advanced. An examination of Richey's data (23, figures 5 and 6, p. 30 and 31) shows that the normal pubertal growth increment is apparent more than 2 years before the advent of axillary hair.

The metabolic effects of 5 mg of estradiol benzoate daily in the eunuchoid resemble those of a comparable amount of testosterone propionate in several respects. There is a general agreement with the find

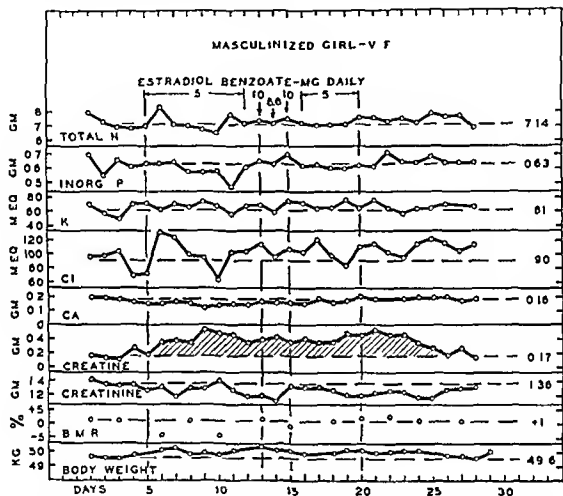


Fig. 7. EFFECTS OF ESTRADIOL BENZOATE given intramuscularly on several urinary constituents, basal metabolic rate and body weight of the masculinized girl *V F* (adreno-genital syndrome). Interrupted lines and the corresponding figures on the right designate pre-treatment baselines. Shaded areas indicate changes in values interpreted as significant.

effects of small amounts of testosterone propionate is duplicated in the growing boy (15) and is accordingly of considerable biologic interest. We have previously discussed our reasons for believing that the androgens exert an important, even though insufficiently defined, somatotrophic influence (4, 5). Many of the metabolic phenomena described here and elsewhere appear to be the chemical manifestations of tissue growth, exemplified by the progressive gains in height and weight of undergrown, underdeveloped boys treated with testosterone propionate (16, 17, 18), methyl testosterone (19, 20) and chorionic gonadotropins (21, 22). It is likely, therefore, that the testicular hormone makes a physiological contribution to the masculine adolescent growth spurt. Since the

ings of Thorn and Engel in the normal male dog and in the woman with Addison's disease (2). The data are given in figures 1, a and 2 for *J X* and in figures 3 and 4 and tables 2 and 3 for *J D*. There was a decline in urinary nitrogen, fairly well defined by the fourth day of treatment, reaching a maximum by the fourth to the eighth day, and sustained often with some irregularity for 10 to 12 days after cessation of the injections. As is often the case with testosterone propionate in the eunuchoid, no evidence of a compensatory loss of urinary nitrogen was obtained during the recovery period. The degree of decline approximated that obtained with 5 mg of testosterone propionate in the same patients. Fecal nitrogen was unaltered (table 3) and the concentration of several nitrogenous

constituents of the blood—blood urea, plasma protein and non-protein nitrogen—was not increased (table 3). In these respects also the response was similar to that characteristic of testosterone propionate (table 1).

As with testosterone propionate, the point of deposit of the retained nitrogen is obscure. Expansion of the extravascular, extracellular fluid compartment of the body even to the full extent of the weight gained would account for only a minute fraction of the nitro-

while nitrogen retention is still proceeding after cessation of treatment. Water retained with sodium and chloride is therefore in all probability largely responsible for the weight increment in brief experiments with estradiol benzoate, just as it is with testosterone propionate.

Urinary inorganic phosphorus consistently declined under the influence of the estrogen in all 4 experiments in the 2 eunuchoids. Fecal phosphorus was unaffected and the concentration of inorganic phos-

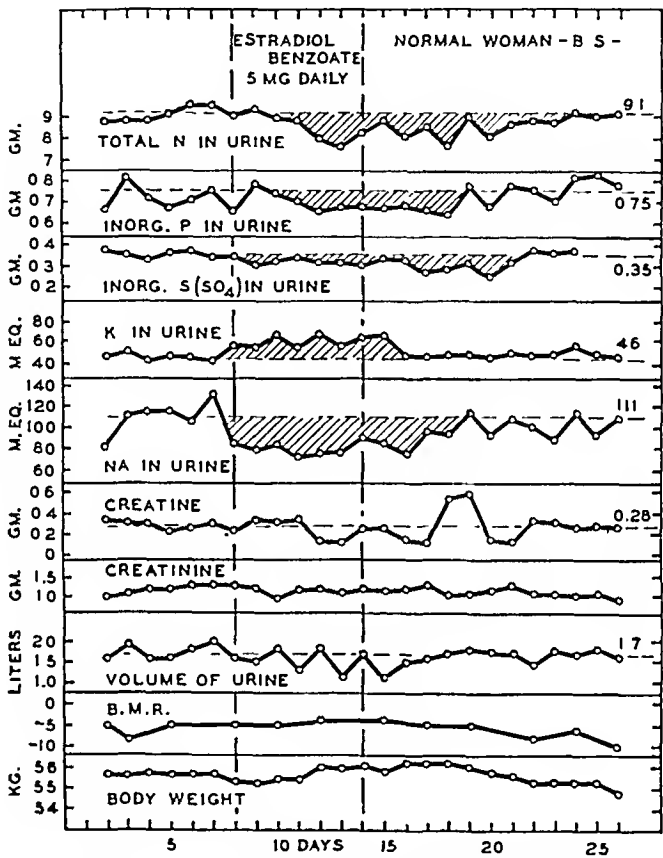


Fig. 8. EFFECTS OF ESTRADIOL BENZOATE given intramuscularly on several urinary constituents, basal metabolic rate and body weight of the normal young woman B. S. Interrupted lines and the corresponding figures on the right designate pre-treatment baselines. Shaded areas indicate changes in values interpreted as significant. Sulfate was determined and is expressed in terms of S.

gen retained (0.14 gm. in J. D., experiment 1). Presumably protein is deposited somewhere and there is now no evidence permitting decision as to whether the locus is the same as with testosterone propionate or not. Obviously, growth of internal female genitalia is not essential for the phenomenon. As with testosterone propionate (4) the amount of body weight gain attributable to retention of protein, with associated water in skeletal or visceral tissue, falls short of accounting for the actual weight gain (300 gm. at day 11, in J. D., fig. 3 as compared to 800 gm. of actual gain). Furthermore, weight is commonly lost

phorus in the serum was not increased (tables 2, 3). Neither urinary nor fecal calcium nor the calcium content of the serum were affected (figs. 3, 4, table 3). These reactions were similar qualitatively and quantitatively to the response to testosterone propionate (fig. 1, b, 3; tables 1, 2, 3). While the influence of estradiol benzoate on inorganic phosphorus metabolism in these subjects is in agreement with the results of Thorn and Engel on the normal male dog and the woman with Addison's disease, and those of Albright, Bloomberg and Smith in women with osteoporosis, the latter group demonstrated notable cal-

cium retention in their subjects. Either the osteoporotic women were especially sensitive to the calcium retaining properties of estradiol benzoate or the length of our periods of treatment was insufficient to develop this effect, despite our substantially heavier dosage. Since the maximum calcium retention in the women with osteoporosis occurred at about 20 days, more protracted study of the eunuchoid is obviously necessary. Within the limits of our experimental periods, however, retention of inorganic phosphorus seems more likely to be correlated with that of nitrogen than with that of calcium.

In *J D* (fig. 4) urinary sulfate declined during treatment with estradiol benzoate. This was not as conspicuous however as with the same dose of testosterone propionate (fig. 3) and was hardly apparent in the other experiment on this same subject (fig. 3).

The consistent sharp decline in urinary sodium excretion in all 4 experiments on the eunuchoids is in agreement with the repeated demonstration by Thorn and his coworkers of the sodium retaining action of estradiol in both dogs and man (1, 2, 24). As in the experiments with testosterone propionate, sodium diuresis occurs in the early phases of the recovery period while nitrogen retention is still going on. While the extent of the decline in urinary sodium excretion may somewhat exceed that induced by testosterone propionate (*J X*) the difference is not as great as in the dog in which testosterone has little or no sodium retaining action (2).

Urinary potassium excretion is judged uninfluenced by the estrogen. In *J D* (fig. 3) the initial baseline is probably too high by virtue of two values at the beginning of the experiment, and the comparison of the treatment period with the recovery baseline indicates no decisive influence. This is in agreement with the results of the other three experiments (*J X*, fig. 1, a, 2, *J D*, fig. 4). Five mg. of testosterone propionate may (*J D*, fig. 3) or may not (*J X*, fig. 1, b) reduce urinary potassium excretion. This response is usually distinct with 25 mg. daily.

An increase of 1 to 1.5 kg. in body weight may occur as a result of treatment with estradiol benzoate (*J X*, fig. 1, a, 2, *J D*, fig. 3) or may not be apparent (*J D*, fig. 4). This gain in weight must be due largely to water retention, presumably chiefly in association with retained salt, as previously noted. In some experiments (*J X*, fig. 2) urine volume is sharply reduced during treatment to rise thereafter, in others (*J X*, fig. 1, a) the variations in urine volume are less satisfactory, presumably because uncontrolled forces modifying water metabolism exert complicating influences.

When creatinuria was sustained at high levels by creatine ingestion in *J D* no reduction in the amount excreted was obtained when estradiol benzoate was

given (fig. 3, 4). This is in distinct contrast to the depression of exogenous creatine excretion by 5 mg. doses of testosterone propionate (fig. 3). Jailer's experience (25) in the male monkey was similar, although the amount of this estrogen (100 R U, 0.017 mg.) was not as large as that of the androgen (2-5 mg.). Kun and Pecznik (27) likewise describe the creatinuria of the castrated male rat as reduced by 'proviron' but not by 'progynon,' and Schittenhelm and Buhler (28) suggest the same difference in the hypogonadal human male receiving small amounts of the sex hormones orally. At first thought one is inclined to relate reduction of creatinuria to an improvement in the metabolism of muscle and to suppose accordingly that testosterone has an advantage over estradiol in this regard. Such a supposition would be in agreement with the observation of Papanicolaou and Falk (26) that testosterone propionate, but not urinary estrogens ('amniotin') would induce hypertrophy of the temporal muscle of the castrated male or normal female guinea pig. While this interpretation may be correct, recent studies of Wilkins, Fleischmann and Howard (20) indicate that the effects of androgens on creatine metabolism are more complex than they first appeared to be. In underdeveloped dwarfish boys retaining nitrogen and growing under the influence of oral methyl testosterone, creatine excretion on a creatine free diet substantially increased in time. The question arises as to whether the enhanced creatinuria in their subjects, in which there was every reason to suppose a characteristic metabolic effect of androgens, was due to the use of methyl testosterone rather than testosterone propionate. Until this matter is settled by experiment, we do not feel that we can force the concept of obligatory association between the effects of androgens on muscle and reduction in excretion of ingested creatine.

No distinct effect on basal heat production was induced by estradiol benzoate in the eunuchoid *J D* but small amounts of testosterone propionate likewise fail to make much difference in the relatively brief periods studied here.

The effects of 5 mg. of estradiol benzoate, daily, in the sexually underdeveloped short girl, A B, resemble very closely those in the eunuchoids. Urinary nitrogen, inorganic phosphorus and sodium excretion were depressed, the last temporarily, while potassium excretion was unaffected (fig. 5). Sulfate excretion was probably depressed, but the return to the baseline during recovery was insufficiently decisive. There was no change in the concentration of serum sodium, potassium, inorganic phosphorus or packed red cells. A slight depression in concentration of blood urea nitrogen is suggested (table 4). The data on the effects of progesterone charted will not be discussed as we

have not as yet secured repeatable metabolic effects in man with this steroid.

A. B. belongs to the group of dwarfish, sexually immature women with high urinary gonadotropin titers described recently by Varney, Kenyon and Koch (13) and by Albright, Smith and Fraser (32). It is of interest that her capacity to retain nitrogen was excellent, despite her moderate limitation of growth. In a second individual of this type (R. F.) testosterone propionate, 25 mg. daily, intramuscularly, is seen to exert its characteristic metabolic effect (fig. 6).

When ovarian insufficiency, however, is accompanied by evidences of gross masculinization, estradiol benzoate may exert little or none of its usual action. V. F. was a masculinized girl of 20 with enlarged clitoris, hypoplastic breasts and uterus, amenorrhea, deep voice, masculine hair distribution, firm, well-developed musculature and short stature due to premature ossification of epiphyseal cartilages of the long bones. At this time she excreted 61 mg. of 17-ketosteroid material per day (colorimetric) and 50 i.u. of estrone equivalents per day. Previous surgical exploration, with biopsies of both ovaries showed ovarian tissue present but had not demonstrated an adrenal tumor. It is likely, however, that her adrenals were the source of the excessive androgens. V. F. (fig. 7) gave no distinct evidence of response in urinary nitrogen, inorganic phosphorus or chloride to estradiol benzoate even when the dose was elevated to 26.6 mg. in 3 days. The concentration of several blood constituents was unaltered (see protocols). There was no growth of breast tissue in the 16 days of treatment with the estrogen, nor was there any withdrawal bleeding thereafter, this subject contrasting in both respects with A. B. It may be inferred that V. F.'s indigenous hormones interfered with metabolic response to estradiol benzoate. This interference could be by some direct or indirect endocrine mechanism, or simply by virtue of exerting metabolic influence to the limit of the organism's capacity for response. The suppression of estrogen effect was not complete however in all respects. Diethylstilbestrol, 1 mg. daily in the hands of our colleague Dr. M. E. Davis eventually induced substantial growth of breast buds in this girl.

The increase in urinary creatine during the course of estradiol benzoate treatment in V. F. constitutes an, as yet, isolated observation. It was certainly not apparent in the study of the normal woman B. S. Urinary creatinine in V. F. may have been irregularly decreased at this time, although one naturally hesitates to rely too much on minor changes in creatinine excretion. This phenomenon of heightened creatinuria requires confirmation and further study before speculations as to its mechanism can be usefully entertained.

The effects of 5 mg. of estradiol benzoate daily were studied in a normal young woman (B. S., fig. 8) in the interval between menstrual periods. Characteristic reduction in urinary excretion of nitrogen and inorganic phosphorus was induced. Urinary inorganic sulfate declined slightly. Sodium and chloride excretion declined, effects more likely due to the large amount of added estrogens than to the smaller amounts of endogenous hormones. The well-defined rise in urinary potassium excretion in this subject is anomalous. We have not seen it elsewhere, but hesitate to regard it yet as characteristic of the normal woman. The increase in body weight seems distinct. There was no change in basal heat production. Creatine and creatinine excretion in the urine were judged unaffected. There is accordingly no evidence that normal feminine hormones modify the reaction of the organism to estradiol benzoate, if one excepts the curious data on urinary potassium excretion. We have previously noted that the normal young woman either might give the usual metabolic response to 25 mg. of testosterone propionate daily or might respond indistinctly in several respects (5). Urinary potassium showed no exceptional behavior in this earlier work.

It may be concluded that estradiol benzoate, when administered in sufficient amounts to sexually underdeveloped men, to sexually underdeveloped women with little or no maturation of secondary sex characters and to normal women shares several of the metabolic properties of testosterone propionate. Retention of nitrogen, inorganic phosphorus and sodium may be induced with either substance. In other respects some differences may exist. Urinary potassium excretion was not affected by 5 mg. of estradiol benzoate daily save in the normal woman in whom it was increased. Testosterone propionate always reduces urinary potassium as far as we know, if it affects it at all, but this influence may not always be apparent with 5 mg. daily. While urinary sulfate was not always conclusively depressed by estradiol benzoate, there are sufficient suggestions of this effect to exclude emphasis on this point as a decisive distinction. No evidences of increased heat production due to estradiol benzoate have been secured, but 5 mg. of testosterone propionate daily will often not increase heat production in relatively brief periods of treatment. Creatinuria, when sustained at high levels by creatine ingestion in the eunuchoid, was not depressed by estradiol benzoate as it was by testosterone propionate. Tentatively, this seems a valid distinction between the properties of these two substances but it cannot serve as yet to differentiate the metabolic effect of the estrogen from that of all androgens. As previously noted, methyl testosterone given orally will enhance creatinuria in undergrown underdeveloped boys (20). Thus, none of the metabolic effects of

androgens demonstrable in hypogonad individuals can as yet be held to be consistently and exclusively associated with the androgenicity of these steroids

Both in this paper, and elsewhere, we have attempted to relate the anabolic effects of the androgens in man to processes of somatic tissue growth. Unfortunately, the term 'somatotrophic' which we have used, must still be used loosely as the sites of new tissue deposit in man are difficult to ascertain precisely. The question now arises as to whether the somewhat similar metabolic properties of the estrogens justify the hypothesis that the ovary as well as the testis exerts an anabolic influence on non genital tissues in man. Albright, Bloomberg and Smith (8) have already suggested such an anabolic action of the estrogens on the bone matrix of osteoporotic women, accounting thus secondarily for the retention of calcium and phosphorus induced. The data given here for the eunuchoid make it sufficiently clear that growth of female genitalia does not solely determine the retention of such constituents of tissue as nitrogen and phosphorus. It is thus well within the realm of possibility that the estrogens normally exert a somatotrophic influence during the growth period in man. Sufficient attention has not as yet been given replacement doses of the estrogens, however, to permit judgment as to the likelihood of such an influence. The amounts of androgens which exhibit anabolic effects are small in physiologic terms. The corresponding amounts of estrogens are grossly above physiologic levels. W. M. Allen (29) has estimated that only 5 mg. of estradiol benzoate given over 3 weeks of time are necessary to prepare the uterus of the castrated woman for withdrawal bleeding. This is about one-twentieth of our dosage. The careful studies of Johnston, using estrone in the growing girl, certainly do not encourage the view that small amounts of estrogens produce measurable nitrogen and calcium retention. Nor could Sherman, Gillett and Pope (30) demonstrate periodic fluctuations of nitrogen or phosphorus metabolism during 3 menstrual cycles in 2 normal women. Thorn and his coworkers (31) have suggested that the salt and water-retaining properties of the sex hormones are responsible for the conspicuous periodic gains in weight of some menstruating women. Thorn and Emerson (24) however speak of special predisposing influences in such individuals. The entire matter of the general metabolic rôle of physiologic amounts of ovarian secretions in man therefore must be kept open, pending detailed quantitative study.<sup>5</sup>

The rôle of ovarian hormones in somatic growth is

<sup>5</sup> Dr. Ephraim Shorr has kindly furnished published data of his demonstration that physiological doses as judged by nitrogen retention in amenorrheic girls and young women

of especial importance in interpreting the mechanisms of the shortness of such girls as A. B. and R. F. who have manifest ovarian insufficiency and such high values of urinary gonadotropins as to indicate that their anterior pituitaries secrete as much gonadotropic material as those of the normal woman. Varney, Kenyon and Koch (13) and Albright, Smith and Fraser (32) have discussed this problem and called attention to the largely neglected series of German necropsies in which shortness of stature and ovarian aplasia were associated. Varney and his coworkers noted that the tallness of certain hypogonad women rendered Rossle's hypothesis (33) that the ovaries were essential for the attainment of normal stature difficult to accept, but pointed out that ovarian insufficiency might be of importance in cases where the growth endowment of other origin was imperfect. The present studies demonstrate that the tissues of these people may retain certain of the constituents of protoplasm, either under the influence of estradiol benzoate (A. B.) or testosterone propionate (R. F.). It should be noted that the rôle of feminine androgens as well as of estrogens must be considered in the study of the girl's growth. Wilkins, Fleischmann and Howard (20) observed growth of short poorly developed girls with methyl testosterone, although not with diethylstilbestrol.

In numerous experiments on the growing rat and mouse, estrogens in large amounts have been shown to have a dwarfing effect. Loss of nitrogen accompanies the diabetogenic action of estrogens in rats (34, 35). Nowhere in our work or in that of others, with the possible exception of that of Johnston, has any metabolic influence compatible with such properties been described in man. All human metabolic studies, however, have necessarily been brief and extreme dosages have been avoided. The cessation of feminine growth within a few years after menarche, at a time when high levels of estrogen secretion are sustained by the human ovary, suggests the need for search for properties of the estrogens more compatible with the growth inhibition observed in rodents.

#### SUMMARY

1. Five mg. of testosterone propionate intramuscularly daily in 2 eunuchoids produced characteristic reduction in urinary nitrogen, inorganic phosphorus, sulfate and sodium excretion. In one, urinary potassium was reduced. Creatinuria when sustained at high levels by creatine ingestion, was reduced by the androgen. Basal heat production was unaltered. The eunuchoid organism is thus quite sensitive to the metabolic effects of androgens.

2. Five mg. of estradiol benzoate, intramuscularly daily in 2 eunuchoids, one hypogonad woman and one normal woman induced reduction in urinary nitro-



gen, inorganic phosphorus and sodium excretion. Urinary sulfate was probably reduced in one eunuchoid and in the women. Urinary potassium was elevated in the normal woman. Otherwise it was unaffected. Creatine excretion in the eunuchoid, when sustained at high levels by creatine ingestion, was not reduced by estradiol benzoate. This is in contrast to the effect of the androgen. Basal heat production was unaltered. Several of the metabolic effects of testosterone propionate are shared by estradiol benzoate given in sufficient amounts.

3. A masculinized girl (adreno-genital syndrome) showed none of the usual metabolic effects of estradiol benzoate. Creatinuria was increased.

4. Hypogonad women of short stature and with high urinary gonadotropin titers respond well to the metabolic influences of either estradiol benzoate or testosterone propionate.

5. It is not yet clear that the ovarian secretion in physiologic amounts exerts any general anabolic influence on non-genital tissue.

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# Comparison of Metabolic Effects of Testosterone Propionate with Those of Chorionic Gonadotropin<sup>1,2,3</sup>

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IN A PREVIOUS communication we have noted that several of the metabolic effects of testosterone propionate in the adult eunuchoid could be observed in fairly well defined form with a dosage as low as 5 mg. daily (1, 2). This considerable sensitivity of the organism to the androgen is of great interest since such small amounts of testosterone propionate seem to fall well below requirements for replacement in adults, as nearly as these can be judged by repair of secondary sex characteristics and maintenance of normal urinary androgens (discussed in ref. 1). Since many of these metabolic phenomena appear to be the chemical expressions of non-genital tissue growth (3, 4) it becomes likely that the androgens may play a part in somatic growth at a time when the evolution of secondary sex characters is at least not conspicuous. Normally the boy's pubertal growth spurt is apparent some time before the appearance of axillary hair (5). Well-defined growth in height and weight in boys has now been induced by several observers using testosterone propionate intramuscularly (6, 7, 8) and methyl testosterone orally (9, 10). Chorionic gonadotropin likewise produces an increase in height and weight of boys (11, 12), presumably by virtue of stimulation of the testes. These phenomena were predictable from early clinical studies of the victims of testicular tumors producing androgens (13, 14).

It is therefore quite reasonable that the metabolic

effects of testosterone propionate or methyl testosterone and those of the testicular hormone should coincide. Nevertheless, the identity of the actual secretion of the testis cannot be said to be established, however probable testosterone seems to be as a candidate (15). It is accordingly of importance to compare the metabolic effects of the synthetic agents with those of the testicular hormone itself in some detail. Enhanced testicular secretion may be induced by chorionic material in suitably sensitive immature boys; such a 13 year-old boy, previously shown to be responsive, was utilized in this study. Chorionic material is not known to exert effects on somatic tissues of mammals other than those mediated through the gonads. It has not been possible for us to secure explicit control of this point however by the study of a youthful castrate. The view that any metabolic effects of chorionic material represent the consequences of testicular stimulation only thus remains an assumption, albeit a likely one. The current press of circumstances prevents inclusion of more subjects but the results obtained in the boy R. D. seem sufficiently decisive to record.

## METHODS

The subject, R. D., was studied in the hospital and given a constant diet. The chemical and metabolic methods used have been described previously (2, 4). Aliquots of urine for chemical study were set aside and the rest of the urine was extracted with benzene after hydrolysis for 15 minutes and then separated into neutral (androgenic) and phenolic (estrogenic) fractions (16). Androgens were determined by response of the chick comb, as described by Johnston and Koch (17), 17 ketosteroids were determined on the neutral fraction by Holtorff and Koch's modifica-

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<sup>2</sup> The urinary assays were made possible by a grant from the Committee for Research in Problems of Sex of the National Research Council, and by the Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

<sup>3</sup> The testosterone propionate (Oreton) and chorionic gonadotropin (Pranturon) were provided by Dr. Erwin Schwenk and Dr. Max Gilbert of the Schering Co., Bloomfield, N. J.

tion of the Callow technique (18); estrogens by the method of Varney and Koch using uterine weight in the immature mouse (19). Values for the androgens are expressed in international units (1 I.U. = activity of 0.1 mg. of androsterone); for the 17-ketosteroid in terms of color production equal to that of stated amounts of androsterone; and estrogens in equivalents of estrone (1 microgram equivalent = 10 I.U.)

PROTOCOL

R.D., an intelligent Italian boy, was first seen by us in 1937 when he was 9 years old. He had weighed 7 lb. 3 ounces at birth, following a difficult instrumental delivery. Growth had been slow since; at 9 he was 3 ft. 9.5 in. (117 cm.) tall and weighed 43 lb. (19.9 kg.). There was no family history of dwarfism. Except for bilateral undescended testes no further important defect was apparent on physical examination. His head seemed relatively large and the frontal bones were prominent. A roentgenogram of the sella turcica, repeated in 1941, showed nothing unusual. A series of films of the right hand is available. In 1937, at the age of 9, the epiphysis of the distal ulna, and the greater multangular had not appeared and the lesser multangular and scaphoid were very small. According to Todd's standard (20) his bone age was a little below 6 years. In 1938, at age 10, the ulnar epiphysis and the greater multangular had appeared and enlargement of all carpal bones was distinct. His status was about 7 years and 3 months according to Todd. In 1939, at 11, only the pisiform was absent. In 1941, at 13, all carpal bones were present and of good size, and the only evidence of departure from the standard lay in the relative lack of compact disposition of the carpal bones. Age is difficult to estimate at this time but a retardation of two years may have been present. A steady, if delayed, growth and maturation had proceeded through the years of observation. His growth in height of 21 cm. in 4.5 years, as compared to an average normal growth of about 25 cm., is in accord with this. Dentition departed somewhat from this picture, being well in advance of schedule, even at the age of 9. Dr. Blayney noted, for example, that the cusp of the lower left second molar could then be felt beneath the soft tissue indicating imminent eruption of a tooth not usually present before 12. The incisal halves of the central incisors were hypoplastic, indicating defective calcification at one period in his childhood. This defect was not apparent elsewhere.

Fundi and visual fields were not abnormal. Basal metabolic rates of +29 and +15 (Mayo Foundation standards) at 9 were not in accord with the clinical findings. Numerous subsequent determinations ranged from +2 to -9.

A urea clearance at the age of 13 was  $36 \left( \frac{U}{B} \sqrt{V} \right)$ , slightly below a normal range of 40 to 65. Blood urea N was 10.5 gm. per cent; serum inorganic phosphorus, 5.2 mg. %. The results of urine examination were repeatedly negative. The intravenous insulin tolerance test of Albright, Fraser and Smith (21) was normal in 1941. The serum Wassermann and Kahn reactions were negative,

and red and white cell counts, differential and hemoglobin were normal.

On two occasions previous to the metabolic study recorded here courses of treatment with pregnancy urine extract were undertaken. The first course between July 19, 1937 and February, 1938, resulted in the emergence of the right testis into the inguinal canal and some growth of the phallus. Between March 2 and July 5, 1940, he received 1 grain of thyroid daily. A scant amount of pubic hair was first noted in April, 1940, at the age of 12, and 5 months later a rounded prostate, the area of a nickel, could be felt for the first time. The position of the testis however had not improved and since puberty was appearing spontaneously, it was necessary to proceed with surgery. A preliminary course of chorionic gonadotropin,<sup>3</sup> 150 I.U. 3 times weekly for 2 weeks and 750 I.U. 3 times weekly for 2 weeks, evoking further enlargement and hyperemia of the phallus, did not produce descent of the testes.

On Dec. 18, 1940, Dr. Vermeulen performed the first stage of a bilateral Torek orchidopexy. A large right testis 3 cm. long was found at the internal inguinal ring and a smaller left testis 1 cm. long was located above the internal ring. Fibrous bands investing the spermatic cords were severed and the left spermatic artery and vas deferens freed behind the peritoneum so that both testes could be brought into the scrotum, and anchored to the thighs. The second stage was performed in June, 1941. In the fall of 1941 both testes were in satisfactory position and of normal consistency, the right measured 4 × 3 × 3.4 cm., the left 3.6 × 3.0 × 2.2 cm. The phallus was 6 cm. long, the prostate about 2 cm. in diameter. A small amount of pubic and axillary hair was present. The voice was juvenile. In the year subsequent to the studies reported here the voice deepened decidedly and he grew 4 cm. in height without treatment.

It is not possible at present to account for the subject's short stature. His growth is now proceeding at a fairly normal rate. Some obscure factor operated in early childhood to retard progress temporarily. Malnutrition may have played a part, as his mother spoke of his poor appetite during his childhood. Urinary gonadotropins,<sup>4</sup> gave a value of 20 mouse units per 24 hours in the fall of 1940 when R.D. was 12. This normal figure was to be expected from the spontaneous growth of the patient's prostate gland at that time. Mechanical factors seemed to have impeded testicular descent.

In September, 1941, the boy, then 13, entered the hospital for metabolic study. He was at that time 138 cm. (4 ft. 6 in.) tall and weighed 35.3 kg. (78 lb.). Results of 6 basal metabolic rate determinations ranged from -8 to +2 (Mayo Foundation standards) averaging -5, yielding from 1185 to 1328 Calories per 24 hours, averaging 1238. He was placed on a constant diet of C 266 gm., P 66 gm., F 117 gm., Cal. 2381. This was estimated to contain N 10.6 gm., S 0.59 gm., P 1.28 gm., Ca 1.28 gm., K 3.65 gm. and Na 1.07 gm. To this 4 gm. of NaCl was added at the table. The fluids, including distilled drinking water, were kept constant in composition and amount

<sup>4</sup> The urinary gonadotropins were determined by R. F. Varney of the Department of Biochemistry.

(1850 cc daily) He attended school regularly, taking his prepared lunch and carrying a bottle for one unnation at home at noon. We are greatly indebted to both the boy and his mother for their patient cooperation. The values for the urinary creatinines were reasonably consistent and it is believed that there were no serious errors. There was insufficient time on school mornings for breakfast, basal metabolic rates and school so that we have insuff-

depression of urinary inorganic phosphorus, sulfate, potassium and sodium is as great in the 13-year old boy if allowance is made for the greater variability of these effects. Creatinuria was depressed by testosterone propionate as it was in several eunuchoids showing considerable amounts of creatine in the urine while on a general diet (3) or ingesting creatine (2, 4).

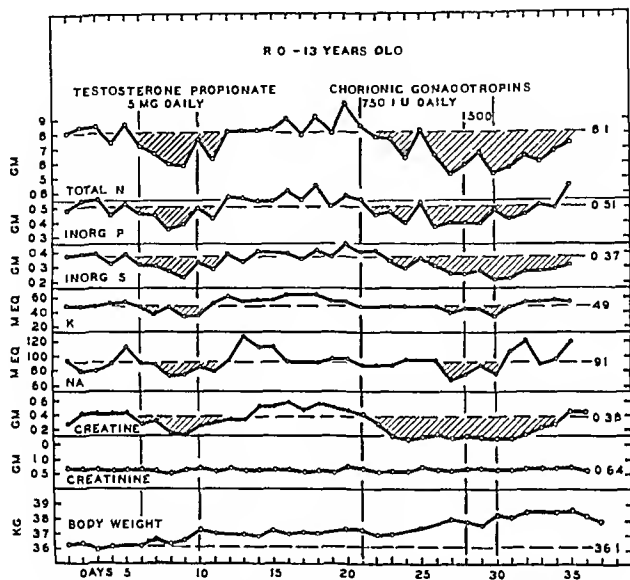


Fig 1 Comparative metabolic effects of testosterone propionate and chorionic gonadotropin on R D, a short but growing boy in the early phases of spontaneous puberty

ficient data on heat production during the course of treatment. Scattered readings are listed according to the days in figure 1 and provide no evidence of significant change.

| Day | B M R | Cal per Hour | R Q  |
|-----|-------|--------------|------|
| 4   | +2    | 55.4         | 0.80 |
| 11  | -3    | 53.7         | 0.81 |
| 18  | -7    | 51.5         | 0.86 |
| 25  | +0    | 55.3         | 0.80 |
| 32  | +2    | 57.2         | 0.80 |

#### DISCUSSION

R D, a short but growing 13 year old boy with a few signs of early puberty, responded in much the same manner to 5 mg of testosterone propionate daily (fig 1) as do adult eunuchoids to this amount (1, 2) or more (3, 4). The 45 mg of nitrogen retained per kg per day at the time of maximum effect of the androgen corresponds very closely to the 27 to 41 mg recorded for the 3 eunuchoids receiving an identical dose, the

This point is of interest in view of Duckworth's finding that the creatine tolerance of normal boys in the age range of 7 to 15 years could not be altered by testosterone propionate (22). R D's weight increased at the usual time during treatment and to the usual extent but the baseline was not resumed on cessation of the injections, and the entire effect may be considered blurred by his tendency to gain weight throughout the experiment. As noted in the protocol, scattered readings indicated no modification of basal heat production or of the respiratory quotient.

Chorionic gonadotropin, 750-1500 i.u. per day, induced a general metabolic response in R D, the pattern of which corresponds very well to that observed with testosterone propionate. The more gradual return of the affected urinary constituents toward the baseline on cessation of treatment with the gonadotropin is not to be stressed. In numerous ex-

periments with testosterone propionate previously undertaken here (2, 3, 4) the resumption of baseline values has required more time than in *R. D.* It is not clear, however, that the effects of chorionic gonadotropin correspond precisely to those of methyl testosterone given orally. While methyl testosterone produces distinct reduction in urinary nitrogen, inorganic phosphorus, sodium, potassium and chloride (9, 10) Wilkins, Fleischmann and Howard (10) have clearly shown that it will, in time, increase creatinuria in the boy on a creatine-free diet. While much more detailed comparison between testosterone propionate and methyl testosterone is necessary in this regard, the present experiment suggests that the testicular secretion may differ from methyl testosterone in its influence on creatine metabolism.

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE AND CHORIONIC GONADOTROPIN ON URINARY STEROIDS OF *R. D.*

| Day     | No. days | Androgens, I.U./day | 17-ks., mg./day | Estrogens, $\mu$ g. estrone/day |
|---------|----------|---------------------|-----------------|---------------------------------|
| Control | 6        | 4-6                 | 7.2             | 1                               |
| Control | 12       | 6                   | 6.2             | <0.5                            |
| 7-10    | 4        | 6                   | 5.7             | <1                              |
| 11-16   | 6        | 6                   | 4.8             | 1                               |
| 17-20   | 4        | 7                   | 5.4             | 1-2                             |
| 22-27   | 6        |                     | 7.6             | 0.5                             |
| 28-30   | 3        | 5-6                 | 6.6             | <0.7                            |
| 31-36   | 6        |                     | 4.6             | 0.6                             |
| 37-41   | 5        |                     | 4.6             | 0.2                             |

Five mg. of testosterone propionate was given daily from day 6 through day 10; 750 I.U. of chorionic gonadotropin was given daily from day 21 through day 27, 1500 I. U. of chorionic gonadotropin was given daily from day 28 through day 30. The numeration of days corresponds to that in figure 1.

The amount of nitrogen retained under the influence of chorionic gonadotropin at the time of maximum effect is 65. mg. per kg. per day. This is somewhat greater than was secured with 5 mg. of testosterone daily in *R. D.* or in the 3 eunuchoids studied. It corresponds very well with the 63 mg. per kg. per day average (range 51-83) for 6 experiments in 5 eunuchoids receiving 25 mg. of testosterone propionate daily. The individual variation in the degree of influence exerted by testosterone propionate on other urinary constituents is greater than with nitrogen. It is often difficult to relate the extent of effect to dose or to secure greater consistency by taking body weight into account. One may, however, say that the effects of chorionic gonadotropin are as substantial as those of 5 mg. or more of testosterone propionate daily. The rather insignificant reduction in urinary potassium with the chorionic material may be matched by

the complete absence of effect of 5 mg. of testosterone propionate in the eunuchoid *J. X.* (2) A comparative table of the data on several subjects is given in another paper (23).

We regret that we are unable to present data on calcium metabolism. It is highly desirable that this be undertaken. The growth in height and development of bone described in children receiving several androgens and chorionic gonadotropin attests to the eventual deposit of calcium salts in these individuals. Calcium retention has been clearly shown to occur under the influence of testosterone propionate in Cushing's syndrome (24) and in an aged man with osteoporosis (25) and is to be expected in the child given sufficiently protracted study.

Table 1 shows that the urinary excretion of 17-ketosteroids, of androgens and of estrogens was unaltered during treatment with either testosterone propionate or chorionic gonadotropin. It has been abundantly demonstrated that the larger amounts of testosterone propionate will produce notable increases in urinary androgens (26-29). Fewer data are available concerning small doses. Holtorff and Koch (18), however, have recorded both colorimetric and biologic assays on the urine of our eunuchoid *J. K.* (1) while he was receiving 5 mg. of testosterone propionate daily. His control levels were 21. I.U. of androgenic activity and 6 mg. of 17-ketosteroids per day. During 15 days of treatment he averaged 43 I.U. and 8.5 mg. per day. This represents a 52 per cent recovery of the injected testosterone, if the urinary androgen be assumed to be androsterone and a 60 per cent recovery as a 17-ketosteroid. The values for recovered biologic activity are somewhat, but hardly seriously, above those found when 20 to 25 mg. of testosterone propionate are given daily to hypogonad men, if the same assumptions are made in the calculation (27, 28). On any such basis *R. D.*'s biologic assay should have risen 22 I.U. per day and his 17-ketosteroids 2.5 mg. per day. While the latter increase may have been obscured by fluctuations in the day-to-day excretion it seems likely that any such increase in biologic assay would have been detected in view of the constancy of the low androgen values recorded throughout the experiment. We have no explanation at this time for this result. The recovery values in *J. K.* may well be exceptionally high and serve poorly as a guide. In any event, it is of interest that the metabolic effects of both testosterone propionate and chorionic gonadotropin were distinct at times when urinary assays gave no hint of heightened activity of testis hormones in the body. It is likely, therefore, that the testis may make substantial contributions to the growth process in the child, without inducing any measurable urinary representation of such contributions. The appearance of increased

amounts of such a derived steroid as androsterone is not a necessary companion of physiologic response

## SUMMARY

In a 13 year-old boy 5 mg of testosterone propionate daily induced reduction in urinary excretion of nitrogen, inorganic phosphorus, sulfate, potassium, sodium and creatine

Chorionic gonadotropin (750 to 1500 i u) exerted essentially the same effects as testosterone propionate. In several respects the influence was more powerful than that of 5 mg of testosterone propionate daily

The metabolic influences of both agents were unaccompanied by any change in the urinary excretion of androgens, estrogens or 17 ketosteroids

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# Metabolic Response of Aged Men to Testosterone Propionate<sup>1,2</sup>

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IN 1889 BROWN-SEQUARD (1), then 72 years old, injected a testicular extract into himself and experienced a return of his youthful sense of well-being. Since this historically important, though unreliable experiment, Brown-Sequard's guiding idea that the testis might play some decisive rôle in somatic senescence has never been entirely lost sight of, even though it has acquired little substantial support. Such a rôle demands that the testicular hormone exert some important metabolic effect upon non-genital tissues, that hormone secretion be reduced during the declining years and that aged tissue retain sufficient sensitivity to the hormone to make any deficit in secretion one of material consequence.

It is now apparent that testosterone propionate, when given intramuscularly to the hypogonad or normal man or woman, exerts metabolic influences which are compatible with the formation of new non-genital tissue (2-5). Methyl testosterone given orally evokes much the same response, although some differences in detail may exist (6). Although there are many uncertainties concerning the site of this new tissue deposit, and the functional consequences of such effects remain a matter for speculation, we must now regard the testis as exerting a complex anabolic influence in human economy. Thus the Brown-Sequard hypothesis, often seeming the oldest of endocrinological foibles, requires re-examination.

The age of tissue often materially influences the response to hormones. Engle (7) has reviewed this problem with respect to testicular function. Thus, the seminiferous epithelium of the testis of the growing rat responds to gonadotropins with sperm formation only when the animal is old enough (7). Hooker

(8) has described a special enhancement of sensitivity of the seminal vesicles of the castrated rat to androgens at the time of normal puberty. The focal regression of prostatic epithelium of man, beginning in the forties (9) is compatible with diminished androgen production by the testis, but Moore and McLellan (10), unable to detect modification of such tissue by pre-operative administration of testosterone propionate, suggest loss of local sensitivity to the hormone as a decisive factor in senile prostatic atrophy. Carcinomatous prostatic tissue, however, often retains some dependence upon testicular androgens and may regress after castration according to the brilliant and provocative work of Huggins and his associates (11, 12). Since the sensitivity of aged tissue to androgens must be known in order to evaluate the usefulness of any testis hormone available, and to estimate the consequences of any deficit, we have extended our studies on the metabolic effects of testosterone propionate to two old men. Such work is a useful preliminary to the more difficult task of interpreting these chemical effects in terms of the well being of the individual.

## METHODS

The subjects were placed in the hospital and given a constant diet providing sufficient caloric intake to maintain an approximately constant weight and to permit moderate activity about the wards. Metabolic and chemical methods used have been previously described (3, 5) with the exception of that for capillary blood-glucose on *M. L.*, which was determined by the method of Miller and Van Slyke (13).

Through the courtesy of our colleagues in the Department of Biochemistry working under Dr. F. C. Koch we are able to quote assays on the urine of these subjects. The 17-ketosteroids were measured as described by Holtorff and Koch (14); androgens, by the capon's comb, using an inunction procedure soon to be described by Johnston and Koch; estrogens, by induction of estrus in the spayed rat, the details of

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<sup>2</sup> The testosterone propionate used was generously provided by Dr. Erwin Schwenk and Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J.

which are given by Koch (15) Extraction of these steroids was conducted as previously described (16) Gonadotropins in the urine were precipitated by alcohol and assayed by increase in weight of the uterus of the immature mouse (17)

Through the courtesy of our colleague in the Department of Surgery, Dr W W Scott, we are able to quote his determinations of the urinary acid phosphatase on our two aged men The method used, to

Traces of glucose were commonly found in the urine Blood glucose values in mg per cent during a glucose tolerance test follow fasting, 88, 1/2 hour, 194, 2 hours, 211, 3 hours, 174 From + to ++ reduction appeared in the urine in all samples after the fasting specimen This was interpreted as demonstrating a mild diabetes mellitus

A 6-day urine collection showed the presence of 11.3 mg of 17 ketosteroids (colorimetric) and the equivalent of 8 to 9 microgram equivalents of estrone per day These may be taken as normal Urinary gonadotropins were 20

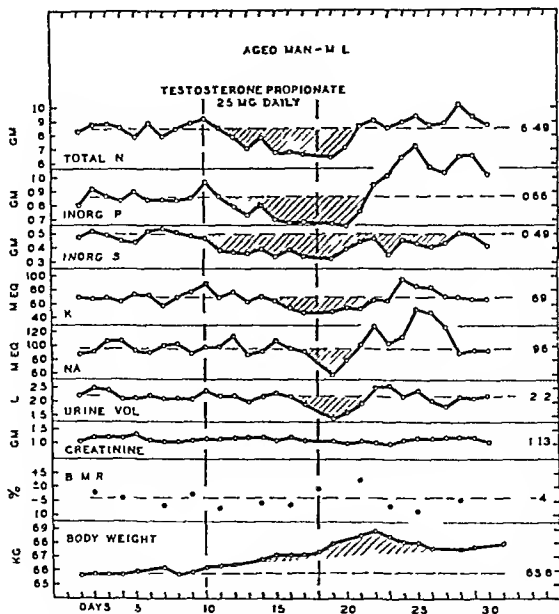


Fig 1 EFFECT OF INTRAMUSCULAR INJECTIONS OF TESTOSTERONE PROPIONATE ON several urinary constituents basal metabolic rate and body weight of the 76-year-old man M L 25 mg was given daily from day 10 through day 18 Sulphate expressed as S was determined

gether with norms at various ages, are given by Scott and Huggins (18) Determinations were made on fresh morning urine

#### PROTOCOLS

ML was a 76 year-old man, a patient of Dr H T Ricketts who kindly permitted us to make these observations Save for a moderate grade of arteriosclerosis, a moderate enlargement of the prostate gland which had provoked no disturbance in the function of the urinary tract and a slight hypertension (150/172/76-90 mm Hg) there were no abnormalities on physical examination The urea clearance was somewhat reduced giving a value of

44  $\left(\frac{UV}{B}\right)$  as compared to a normal range of 60 to 90

to 30 and 50 mouse units per day which likewise may be regarded as normal, the latter value however being a little high

He was studied in January, 1941 At this time the diet comprised C 200, P 72, F 161, Calories 2537 This was estimated to provide 11.5 gm of N, 0.87 gm of S 1.67 gm of P, 1.71 gm of Ca, 3.85 gm of K, 1.27 gm of Cl To this was added 4 gm of NaCl at the table The fluid intake, including distilled drinking water, was maintained at 2900 cc daily The basal metabolic rate, after training averaged -4 (Mayo Foundation standards) yielding 1439 Calories per 24 hours By virtue of a diet somewhat high in calories he gained a little over 2 kg during the month of the experiment, a gain not attributable to the treatment with testosterone propionate As seen in table



little or no hyperglycemia occurred on this regime. Urinary reducing substances were usually absent or present only in traces.

The details of the metabolic influence of testosterone propionate are shown in figure 1 and table. 1. Urinary calcium, which is not so recorded, was uninfluenced by treatment. A 4-day control period (days 6-9) showed 0.054 gm. per day, a 3-day period (days 15-17) showed 0.075 gm per day, and a 3-day recovery period (days 29-31) showed 0.069 gm. per day. The androgen had no

TABLE 1. EFFECT OF TESTOSTERONE PROPIONATE ON VARIOUS BLOOD CONSTITUENTS OF THE AGED MAN, M. L.

| Day             | Blood Urea N<br>mg % | Serum P<br>(inorg)<br>mg % | Glucose in Blood <sup>2</sup><br>mg % at Hours |       |      |      |
|-----------------|----------------------|----------------------------|--|-------|------|------|
|                 |                      |                            | 7:30   | 11:15 | 4:15 | 9:15 |
| 1               | 12.7                 | 3.5                        | 109  | 101   | 113  | 110  |
| 3               | 13.1                 | 3.4                        | 113  | 102   | 108  | 116  |
| 8               | 9.8                  | 3.3                        |  |       |      |      |
| 10 <sup>1</sup> | 11.0                 | 3.6                        | 102  | 113   | 104  | 125  |
| 15              | 8.2                  | 3.5                        | 97   | 101   | 113  | 111  |
| 17              | 7.8                  | 2.7                        | 103  | 103   | 131  | 122  |
| 22              | 10.8                 | 3.6                        | 109  | 119   | 118  |      |
| 24              | 11.2                 | 3.9                        | 103  | 97    | 115  | 120  |

<sup>1</sup> Testosterone propionate 25 mg daily intramuscularly was given from days 10 to 18 inclusive.  
<sup>2</sup> Blood glucose was determined on capillary blood.

effect either on M.L.'s sexual excitability or on his sense of well being. As in our previous work there was no influence on pulse rate, blood pressure or fasting respiratory quotient. These values are, accordingly, not given. Ten control determinations for urinary acid phosphatase averaged 10 units per 100 cc. (range 1.8-20.5). Five determinations during treatment averaged 10 units (range 3.4-25 units). These values are well below those of normal young men, who average about 60 units per 100 cc. (18).

S.F. was a 76-year-old man with a blepharospasm, due in all probability to arteriosclerotic degeneration of the extra-pyramidal brain centers. His physician, Dr. R. B. Richter, kindly permitted these studies. Except for this defect and for an enlarged prostate and lenticular opacities, there was little abnormal on physical examination. The urea clearance was somewhat reduced, giving values of 24 and  $23 \left( \frac{U}{B} \sqrt{V} \right)$  as compared to a normal of 40 to 65.

There was no abnormality of the urine by routine tests. The patient's blood Wassermann reaction was repeatedly strongly positive, the Kahn reaction negative. In view of his age this matter was not pursued further and the syphilis was regarded as latent. A 5-day-urine collection yielded 14 mg. of 17-ketosteroids (colorimetric) per day, 56 I.U. of androgenic activity, and less than 5.5 microgram equivalents of estrone. Urinary gonadotropins were 30 to 40 mouse units per day. These are all normal values.

He was studied in February and March of 1941. The diet comprised C 285, P 58, F 87, Calories 2155, and was estimated to yield 9.3 gm. of N, 0.80 gm. of S, 0.98 gm. of P, 3.4 gm. of K, 1.03 gm. of Na. To this was added 4 gm. of NaCl at the table. The fluid intake, including distilled drinking water, was kept at 2300 cc. daily. The basal metabolic rate, after training, averaged -5 (Mayo foundation standards) giving 1267 Calories per day. Since from 50 to 100 cc. of residual urine remained after urination, each collection period was begun and terminated by catheterization and the urine for each period was pooled for analysis.

The details of the metabolic influence of testosterone propionate are given in figure 2. Values for blood urea nitrogen and serum inorganic phosphorus were normal and unaltered by treatment, and so are not recorded. As in M.L. the androgen had no influence on sexual excitability or sense of well being. Eight determinations of urinary acid phosphatase before treatment averaged 33 units per 100 cc. with a range of 26 to 41. Seven determinations during treatment averaged 38 units with a range of 27 to 49.

DISCUSSION

The data given in figures 1 and 2 and in table 1 on the two 76-year-old men, each receiving 25 mg. of testosterone propionate daily, discloses no sharp variation in pattern from that previously recorded

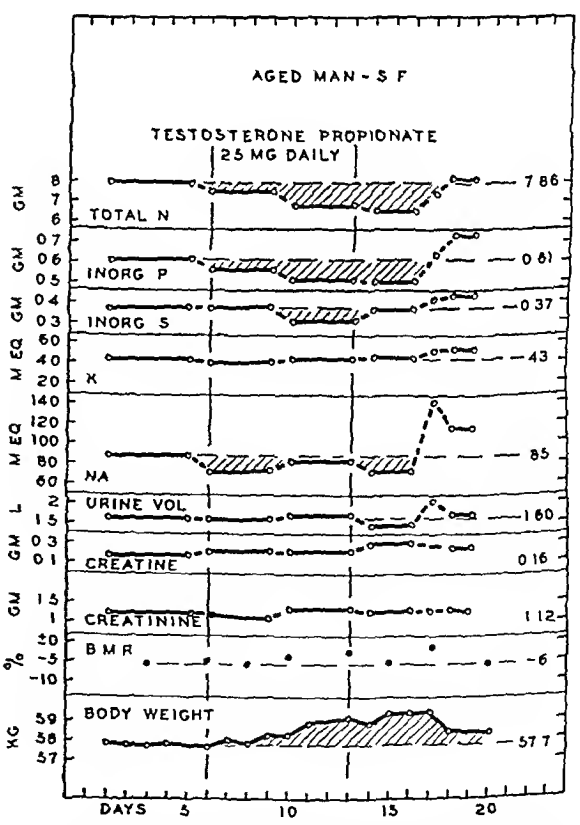


Fig. 2. EFFECT OF INTRAMUSCULAR INJECTIONS OF TESTOSTERONE PROPIONATE on several urinary constituents, basal metabolic rate and body weight of the 76-year-old man S. F., 25 mg. was given daily from day 6 through day 13. Sulfate expressed as S was determined.

for hypogonad men (2, 3, 5) and women (5) and normal men and women (3). The decline in urinary nitrogen and inorganic phosphorus begins promptly and is well sustained. As is often the case in our other subjects the more complete data on M. L. shows no evidence of a conspicuous compensatory loss of nitrogen through the urine after cessation of injections, thus indicating that aged tissue may retain nitrogenous material as tenaciously as more youthful tissue. The

not reduced by testosterone propionate. Even in the eunuchoid, creatinuria of this grade occurring when the patient is on a general diet, may be little influenced by the antrogen (3, fig. 2). The rise in basal heat production expressed either as basal metabolic rate or as total Calories per hour, is only suggestive in M. L. and S. F. under the influence of testosterone propionate. In the eunuchoid the increase in heat production may seem more distinct in the first 10 days

TABLE 2 MAXIMAL REDUCTION INDUCED BY ANDROGEN IN URINARY EXCRETION OF SUBSTANCES

| Subject | Condition               | Age, yr | Weight, kg | Testosterone Propionate, daily mg | N, gm/day | N Retention, gm/kg/day | P, gm/day | P Retention, mg/kg/day | S, gm/day | K, m eq/day | Na, m eq/day | Cl, m eq/day |
|---------|-------------------------|---------|------------|-----------------------------------|-----------|------------------------|-----------|------------------------|-----------|-------------|--------------|--------------|
| J K (4) | Eunuchoid               | 26      | 77         | 1                                 | 3.04      | 0.030                  |           |                        |           |             |              |              |
| J V (5) | Eunuchoid               | 29      | 66         | 1                                 | 1.80      | 0.027                  | 0.10      | 1.1                    | 0.06      | 0           | 21           |              |
| J D (5) | Eunuchoid               | 34      | 76         | 1                                 | 3.13      | 0.041                  | 0.31      | 4.1                    | 0.18      | 17          | 20           |              |
| Average |                         |         |            | 1                                 | 2.66      | 0.031                  |           |                        |           |             |              |              |
| J K (4) | Eunuchoid               | 26      | 77         | 10                                | 4.62      | 0.060                  |           |                        |           |             |              |              |
| J K (4) | Eunuchoid               | 26      | 77         | 21                                | 6.40      | 0.083                  |           |                        |           |             |              |              |
| J R (3) | Eunuchoid               | 27      | 74         | 21                                | 1.14      | 0.070                  |           |                        |           |             | 21           | 22           |
| J X (3) | Eunuchoid               | 27      | 62         | 21                                | 3.77      | 0.051                  | 0.24      | 1.9                    |           |             |              |              |
| N D (2) | Eunuchoid               | 31      | 53         | 21                                | 3.01      | 0.058                  |           |                        |           |             | 23           | 0            |
| N D (5) | Eunuchoid               | 33      | 60         | 21                                | 3.08      | 0.051                  | 0.21      | 3.1                    |           |             |              |              |
| M D (2) | Eunuchoid               | 51      | 50         | 21                                | 3.10      | 0.064                  |           |                        |           |             | 20           | 10           |
| Average |                         |         |            | 21                                | 4.02      | 0.063                  |           |                        |           |             |              |              |
| J K (4) | Eunuchoid               | 26      | 77         | 50                                | 6.23      | 0.081                  |           |                        |           |             |              |              |
| X (3)   | Eunuchoid               | 27      | 61         | 50                                | 2.03      | 0.048                  | 0.20      | 4.8                    |           | 21          | 26           | 20           |
| Average |                         |         |            | 50                                | 4.58      | 0.061                  |           |                        |           |             |              |              |
| J X     | Eunuchoid               | 29      | 61         | 100 <sup>2</sup>                  | 3.23      | 0.050                  |           |                        |           |             |              |              |
| H S (2) | Eunuchoid hypopituitary | 24      | 64.6       | 25 test. Prop                     | 1.59      | 0.025                  |           |                        |           | 13          | 31           | 20           |
| R D     | Short boy               | 12      | 15         | 5 cho. gonadotrop                 | 1.61      | 0.045                  | 0.08      | 2.2                    | 0.09      | 13          | 17           |              |
|         |                         |         |            |                                   | 2.34      | 0.065                  | 0.09      | 2.5                    | 0.13      | 9           | 18           |              |
| J L (3) | Normal man              | 19      | 86         | 21                                | 2.35      | 0.050                  | 0.16      | 1.0                    |           | 17          | 45           | 46           |
| R W (3) | Normal man              | 21      | 56         | 21                                | 1.66      | 0.029                  | 0.20      | 1.1                    |           | 12          | 20           | 18           |
| M L     | Aged man                | 76      | 59         | 21                                | 1.79      | 0.027                  | 0.19      | 1.2                    | 0.14      | 17          | 42           |              |
| S F     | Aged man                | 76      | 58         | 21                                | 1.32      | 0.023                  | 0.11      | 1.9                    | 0.07      | 0           | 13           |              |
| R F (5) | Hypogonad woman         | 24      | 45         | 21                                | 2.52      | 0.056                  | 0.24      | 5.3                    | 0.21      | 14          | 43           |              |
| P J (3) | Normal woman            | 24      | 61         | 21                                | 2.61      | 0.043                  | 0.28      | 4.6                    |           | 10          | 15           | 19           |
| E S (3) | Normal woman            | 31      | 45.6       | 21                                | 0.73      | 0.016                  | 0.12      | 2.6                    |           | 12          | 22           | 18           |

<sup>1</sup> The original data summarized here are given in the references indicated by the figures in parentheses after the patient's initials. The body weight used in the calculations is the average pre-treatment weight.

<sup>2</sup> 100 mg. methyl testosterone.

<sup>3</sup> Chorionic gonadotropin in addition to testosterone propionate.

phosphate diuresis is, on the other hand, more striking than usual in M. L. This may, however, constitute a merely individual peculiarity. Values for urinary inorganic sulfate decline with those for nitrogen and inorganic phosphorus, although the parallelism is not always perfect (S. F., fig. 2). Urinary potassium is reduced in characteristic fashion in M. L. and is unaffected in S. F. Urinary sodium is reduced in both, although at different times, and exhibits the usual sharp post-treatment diuresis in both men. The reduction in urinary volume is well seen in M. L. but not in S. F. Both men show the weight gain previously described in normal and hypogonad men and women. The slight creatinuria of S. F. (200 mg. per day) was

of treatment, but longer periods are often required to demonstrate clearly the calorogenic properties of testosterone propionate (4). No elevation of the concentration of urea nitrogen in the whole blood or inorganic phosphorus in the serum was induced (table 1).

No alteration in the urinary calcium of M. L. (protocols) was produced by the androgen. Similarly in the eunuchoid N. D. (5) neither fecal nor urinary calcium was influenced by testosterone propionate during brief treatment periods. This, however, must not be taken to mean that androgens never influence calcium metabolism in aged men. In a man with senile osteoporosis, Reifstein and his associates (19) in-

duced conspicuous retention of calcium as well as nitrogen and phosphorus with testosterone propionate. Whether calcium retention is determined by pre-existing atrophy of bone, or whether it can be observed in aged or other men with normal bones, who are given sufficiently protracted treatment, remains unsettled.

It is of interest that the blood glucose of *M. L.* was not altered by testosterone propionate (table 1) nor was the slight irregular glycosuria increased. No indication was apparent of the diabetogenic properties of testosterone propionate described by Ingle (20) with massive doses in the partially depancreatized rat on a high carbohydrate diet or by Dolin, Joseph and Gaunt (21) in the partially depancreatized ferret.

The intensity of response of the aged men compared with that of others may be best seen by examining table 2. The variable length of the several experiments can best be taken into account by attention to the maximal effect of the androgen. As pointed out first by Kochakian and Murlin (27) in the castrated dog, any given dose of the androgen exerts its maximal influence on urinary nitrogen excretion within a week to 10 days. Continuation of such dosage, within the limits of experiments thus far undertaken, does not further modify the response. Our experience in man indicates that this rule holds also for urinary inorganic phosphorus, sulfate and potassium excretion. It is not to be supposed that it would obtain indefinitely. Some obscure physiologic mechanism probably eventually terminates retention of these substances. Such limits, however, have never been well defined in our work which has involved treatment periods for as long as 2 months in the eunuchoid (nitrogen only) (4). Thus the maximal effect recorded in table 2 may be regarded as a fairly stable state and suitable for comparison of various individuals. Sodium and chloride excretion in the urine are, on the other hand, so irregular that the maximal effect of the androgen is not well sustained and the recorded figures represent points rather than plateaux.

The amount of nitrogen estimated as retained per kg. per day by our eunuchoids receiving 25 mg. of testosterone propionate per day ranged from 51 to 83 mg. and averaged 63 mg. That for the two normal young men amounted to 29 and 30, respectively. That for the two aged men reached values of 23 and 27 mg. per kg. per day, approximating the retention by the normal young men. Unfortunately no data are available on aged hypogonad individuals, although *M. D.*, a 51-year-old eunuchoid, retained as much nitrogen per kg. as younger eunuchoids. There seems to be no pressing reason for believing that our aged men suffered from gross testicular insufficiency, and hence should be compared with the eunuchoids. Physical

examination did not suggest hypogonadism. *M. L.* had spoken of waning sexual interest but his wife had died not long before; *S. F.* led an active sexual life. The urinary 17-ketosteroids (11.3 and 14 mg.) and the androgens of *S. F.* (56 I.U.) were within the normal range for young men, although such determinations cannot be taken to measure testicular function only. Values for urinary gonadotropins were not abnormally high. The urinary acid phosphatase of *S. F.* was somewhat below average youthful levels and that of *M. L.* distinctly below. This reduction in prostatic function however may have been as much a matter of reduced sensitiveness to androgens as of diminished hormone production. Thus, although our aged men retained somewhat less nitrogen per kg. per day than our eunuchoids, there is not sufficient reason for believing that this difference was solely due to age. The effects of testosterone propionate on the other urinary constituents cited in table 2 similarly seem as striking in our aged men as in other subjects if due allowance is made for the considerable individual variability in response.

It is of interest that the metabolic effects of testosterone propionate in the aged men were distinct at a time when no effect upon the prostatic secretion of acid phosphatase was apparent (see protocols).

The functional significance of the anabolic effects of testosterone propionate in the aged, like that in others, remains to be determined. On the basis of exceptional muscle hypertrophy in the boy with precocious puberty due to interstitial cell tumors (23), of muscular growth in the guinea pig receiving testosterone propionate (24) and of the impression of growth of muscles given by eunuchoids receiving androgens, it seems likely that muscles may be a site of new tissue deposit. Their strength and efficiency may be improved, thereby, but more objective evidence of such improvement is needed. Since data from animal experiments indicate that androgens may induce growth of the liver (25) and kidney (25, 26, 27) these organs may likewise serve as sources of new tissue deposit and modifications of their function must be sought. Reifenshtein and his coworkers (19) see an opportunity to repair atrophic senile bone by the use of testosterone propionate.

The processes of senescence do not seriously impair the capacity of the organism to respond to the metabolic influences of androgens. Such testicular hormones as are secreted may be held effective in this regard. The precise measurement of testicular hormone production is difficult and awaits more precise methods than have been thus far employed. There is accordingly considerable doubt as to the frequency of reduced hormone production by the aged testis (7). Such testicular insufficiency as exists may be ex-

pected to have metabolic consequences which play some part in the physiology of the aged

#### SUMMARY AND CONCLUSIONS

1 Testosterone propionate, 25 mg daily intramuscularly, reduced the urinary excretion of nitrogen, inorganic phosphorus, sulfate and sodium in two 76 year old men and caused an increase in body weight. Urinary potassium was decreased in one subject. Basal heat production was increased slightly, if at all. The pattern of response was much the same as in younger individuals.

2 The amount of nitrogen retained (25 mg per kg per day at the time of maximal effect) equaled that retained by normal young men, and was less than that retained by younger eunuchoids. Other urinary constituents were affected as much in the aged as in younger subjects, if due allowance is made for individual variations.

3 Senescence, accordingly, does not distinctly modify the metabolic response to androgens. Such testicular insufficiency as exists in the aged may be conceived as having metabolic consequences the functional importance of which remains to be determined.

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# Creatinin Excretion in Women: Clinical Significance in Obesity

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THE DAILY EXCRETION of creatinin on a meat-free diet is constant for each individual and is uninfluenced by many external factors (1, 2). Since creatinin originates from endogenous sources, the determination of its excretion values has been advocated as a measure of the active protoplasmic mass in the body. Shaffer believed it to be derived from some special process of normal metabolism taking place largely, if not entirely, in the muscles (3). Recent studies which confirm this view show muscle creatin as the source (4-7), the total being related to the 24-hour urine creatinin output (8, 9). Creatinin excretion, therefore, affords an index of the protoplasmic activity of the muscles and, indirectly, of the total muscle mass assuming this activity to be basal and constant. Folin first observed diminished excretion of creatinin at a given weight in the obese individual, suggesting the validity of the creatinin coefficient (3) as an index of nutrition.

In office practice, the optimal weight estimation of Willoughby (10), based on a number of bone measurements, has proven to be clinically simple and sound (11). As gauged by clinical impressions of results, the accuracy of the method diminishes with increasing weight, erring on the side of a too-severe optimal in the very obese type.<sup>1</sup> Since muscle mass could be expected to follow true skeletal proportions, an examination of the relationship between creatinin excretion and the Willoughby optimal weight appeared to be of interest. The value of a true optimal weight in the calculation of the basal metabolism of children has been demonstrated by the Talbot (12, 13, 14). The formulation of an optimal weight standard based on physiological evidences of muscularity (defined as creatinin optimal weight) assumed added importance in the belief that it would serve better than actual weight in the calculation of basal metabolism of obese individuals, in spite of the existing discrepancies between the relationship of total metabolism to creatinin excretion (15, 16, 17).

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<sup>1</sup> Willoughby points out that the cosmetic optimal may not coincide with the calculated figure because of a frequently disproportionate weight loss in the various parts of the body in the obese person.

## MATERIAL AND METHOD

This study is based on observations in 50 normal women between the ages of 20 and 45 years. Cases of diabetes as well as of thyroid and metabolic diseases other than obesity, *per se* were excluded. Careful clinical study eliminated those with infections, myopathies and diseases of the cardio-renal system. The basal metabolic rate, serum cholesterol, serologic, hematologic and urine examinations were performed in all cases. Urine collections were made at home under strict regulations of diet and activity for 3 successive days. Meat and meat products were prohibited, although milk, cheese and eggs were permitted. Total fluid intake was regulated to no more than 2 quarts daily. The patients were instructed to rest at home and avoid exposure to sunlight. Presence of fever, upper respiratory infection or active allergy disqualified results. Receptacles with preservative were provided and the patient was requested to bring to the office the complete and separate 24-hour urine specimens obtained during the last 2 days of the test. Good coöperation on the part of the patients and the adequate volume of the urine agreed with the consistency of results of the two successive days. Variations greater than  $\pm 10$  per cent were infrequent. Preformed creatinin was determined by the method of Folin (18) on 1 cc. of urine. An average of the 2 successive figures was taken and expressed to the nearest 50 mg.

## RESULTS AND DISCUSSION

The results of creatinin determinations in 50 patients are tabulated in table 1 and expressions for the relationship of creatinin excretion to weight in the normally proportioned (fig. 2) and in the obese woman (fig. 1) were derived. The optimal weights, as calculated by the method of Willoughby, were further correlated with actual values of the creatinin excreted for all of the 50 women (fig. 3). The relationship of these 3 linear equations to each other is demonstrated in figure 4 and a formula for the conversion of the optimal weight from the Willoughby standard to that of the creatinin optimal is presented in figure 5. Twenty-four-hour creatinin excretion

TABLE 1. CREATININ EXCRETION IN 50 ADULT WOMEN. RELATION TO ACTUAL WEIGHT, WILLOUGHBY WEIGHT ESTIMATION AND CLINICAL IMPRESSION

| Wt. Range<br>lb | Case<br>No | Creatinin, mg<br>per 24 hr | Actual<br>Weight,<br>lb | Willoughby<br>Weight<br>Estimation<br>lb | Height,<br>in | Bone<br>Diameter | Weight<br>Impression |
|-----------------|------------|----------------------------|-------------------------|--|---------------|------------------|----------------------|
| 100-120         | 1          | 700                        | 94                      | 110                                      | 61            | Small            | Underweight          |
|                 | 2          | 800                        | 108                     | 110                                      | 59            | Average          | Plump                |
|                 | 3          | 800                        | 112                     | 100                                      | 63            | Small            | Plump                |
|                 | 4          | 850                        | 108                     | 110                                      | 62            | Average          | Normal               |
|                 | 5          | 900                        | 102                     | 110                                      | 64            | Average          | Underweight          |
|                 | 6          | 1000                       | 110                     | 120                                      | 68            | Broad            | Normal               |
|                 | 7          | 1000                       | 109                     | 100                                      | 64            | Broad            | Normal               |
|                 | 8          | 1000                       | 115                     | 115                                      | 62            | Average          | Normal               |
|                 | 9          | 1000                       | 107                     | 110                                      | 64            | Small            | Normal               |
|                 | 10         | 1000                       | 100                     | 115                                      | 66            | Average          | Underweight          |
|                 | 11         | 1000                       | 113                     | 110                                      | 61            | Average          | Plump                |
|                 | 12         | 1050                       | 116                     | 115                                      | 64            | Average          | Normal, hirsute      |
|                 | 13         | 1050                       | 105                     | 110                                      | 65            | Average          | Normal               |
|                 | 14         | 1100                       | 106                     | 110                                      | 66            | Average          | Normal               |
|                 | 15         | 1100                       | 110                     | 100                                      | 61            | Small            | Plump                |
|                 | 16         | 1150                       | 115                     | 115                                      | 64            | Average          | Normal               |
|                 | 17         | 1150                       | 118                     | 120                                      | 66            | Average          | Normal, hirsute      |
|                 | 18         | 1250                       | 100                     | 110                                      | 61            | Broad            | Underweight, hirsute |
| 120-140         | 19         | 850                        | 136                     | 130                                      | 65            | Small            | Plump                |
|                 | 20         | 850                        | 135                     | 120                                      | 64            | Small            | Plump                |
|                 | 21         | 950                        | 130                     | 110                                      | 62            | Average          | Plump                |
|                 | 22         | 1000                       | 115                     | 115                                      | 65            | Average          | Normal, hirsute      |
|                 | 23         | 1100                       | 122                     | 125                                      | 64            | Average          | Normal               |
|                 | 24         | 1100                       | 116                     | 115                                      | 60            | Small            | Normal               |
|                 | 25         | 1100                       | 124                     | 120                                      | 65            | Average          | Normal               |
|                 | 26         | 1150                       | 132                     | 125                                      | 64            | Broad            | Plump                |
|                 | 27         | 1150                       | 123                     | 130                                      | 68            | Small            | Normal               |
|                 | 28         | 1150                       | 134                     | 130                                      | 66            | Average          | Normal               |
|                 | 29         | 1200                       | 123                     | 120                                      | 66            | Average          | Normal               |
|                 | 30         | 1300                       | 132                     | 125                                      | 66            | Average          | Normal               |
| 140-160         | 31         | 1100                       | 164                     | 120                                      | 62            | Small            | Obese                |
|                 | 32         | 1100                       | 160                     | 125                                      | 62            | Small            | Obese                |
|                 | 33         | 1200                       | 148                     | 106                                      | 62            | Broad            | Obese                |
|                 | 34         | 1250                       | 148                     | 140                                      | 66            | Broad            | Normal               |
|                 | 35         | 1250                       | 143                     | 125                                      | 66            | Small            | Obese                |
|                 | 36         | 1350                       | 154                     | 120                                      | 63            | Average          | Obese, hirsute       |
|                 | 37         | 1350                       | 143                     | 125                                      | 65            | Average          | Obese, hirsute       |
|                 | 38         | 1400                       | 149                     | 130                                      | 63            | Broad            | Obese                |
|                 | 39         | 1850                       | 152                     | 140                                      | 68            | Broad            | Obese, hirsute       |
| 160-180         | 40         | 900                        | 162                     | 130                                      | 63            | Small            | Obese                |
|                 | 41         | 1000                       | 177                     | 120                                      | 64            | Small            | Obese                |
|                 | 42         | 1050                       | 163                     | 140                                      | 63            | Broad            | Obese                |
|                 | 43         | 1400                       | 172                     | 146                                      | 69            | Broad            | Plump                |
|                 | 44         | 1450                       | 162                     | 135                                      | 67            | Broad            | Obese, hirsute       |
| 180-200         | 45         | 1100                       | 184                     | 125                                      | 64            | Small            | Obese                |
|                 | 46         | 1150                       | 203                     | 150                                      | 63            | Small            | Obese                |
| 200-220         | 47         | 1400                       | 200                     | 145                                      | 61            | Small            | Obese                |
|                 | 48         | 1450                       | 214                     | 140                                      | 62            | Broad            | Obese, hirsute       |
| 220-plus        | 49         | 1700                       | 245                     | 140                                      | 65            | Broad            | Obese                |
|                 | 50         | 1550                       | 279                     | 142                                      | 66            | Broad            | Obese                |

values in the well proportioned individuals form the standard for determination of the creatinin optimal weight. The relation of the optimal weights, based on the Willoughby bone measurements, to creatinin excretion is not identical with the above. The lines cross each other at 123 pounds, the Willoughby figures presenting a smaller range, being too liberal at the lower weight figures and too severe at the

higher. Practical experience with results in induced weight loss justified an arbitrary addition of 10 to 20 pounds to the Willoughby figure for best cosmetic results, thus approximates the creatinin optimal standard. The above two equations are valid for more than 80 per cent of the cases if a variation of 150 mg of creatinin at a given weight is admitted.

Weight for weight, the obese individuals excreted

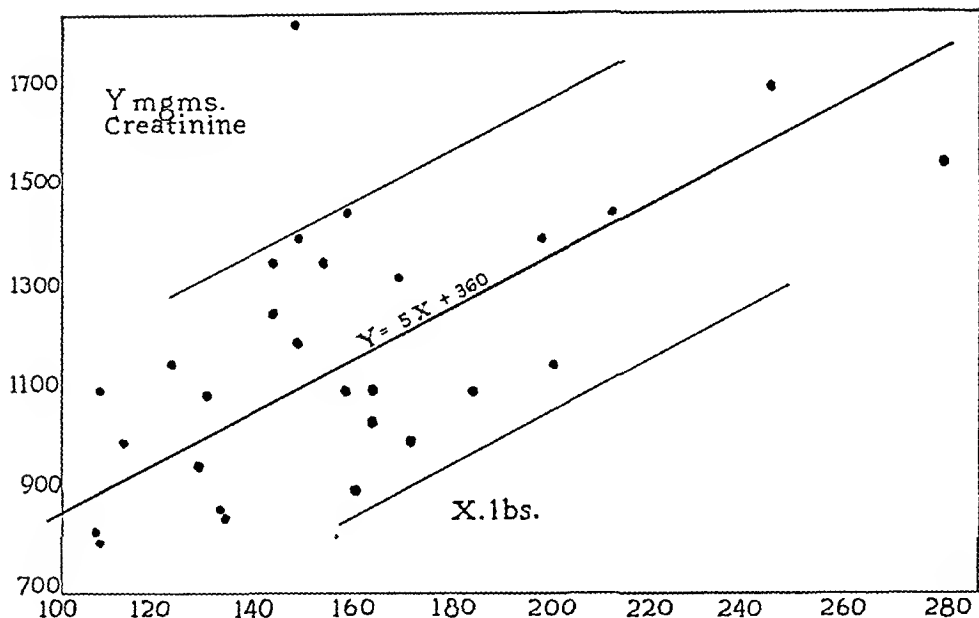


Fig. 1. RELATIONSHIP OF CREATININ EXCRETION (Y) TO WEIGHT (X) in obese women. Variations of  $\pm 280$  mg. true for 96 per cent of all values.

considerably less creatinin than the well-proportioned ones. Formulation of a linear expression (relationship of actual weight to creatinin excretion) in the obese women can be made with less certainty because of the striking variations in creatinin excretion from one individual to another at a given weight. When the same variation ( $\pm 150$  mg. of creatinin at a given weight) is admitted for this group as for those previously studied, the formula included only 42 per cent of the obese cases, thus disqualifying the observation. A variation of about  $\pm 280$  mg. must be admitted to permit a formulation here at all. A characteristic feature of obesity, therefore, is not only the lowered creatinin excretion in most of the cases, but also the great variability from one individual to another, depending on clinical evidence of muscularity. It may be added that the presence of hirsutism appears to influence creatinin excretion, i.e., there is a greater output of creatinin probably because the hirsute individuals frequently are more muscular. Generally speaking, the degree of muscularity of the individual can be correlated with the levels of creatinin excretion

(20, 21, 22). The finding of diminished creatinin excretion in the obese group, as a whole, supports this observation because, weight for weight, the obese individuals are less muscular. Conversely, there are a good many obese women who are more muscular than is apparent. Since the degree of muscularity is not always easily ascertained in the heavy female, creatinin excretion may be used as a valuable index thereof. The wide variations in creatinin excretion levels from one individual to another is to be emphasized, because it indicates that wide variations of muscularity or its physiological activity do exist. The total resting metabolism of the obese individual is known to be elevated (23, 24). The metabolic activity due to fat accounts for a small fraction of this increment, the remainder being due to the metabolic activity of the protoplasmic mass of other tissue (25). Thus, the presence of excess body fat requires in-

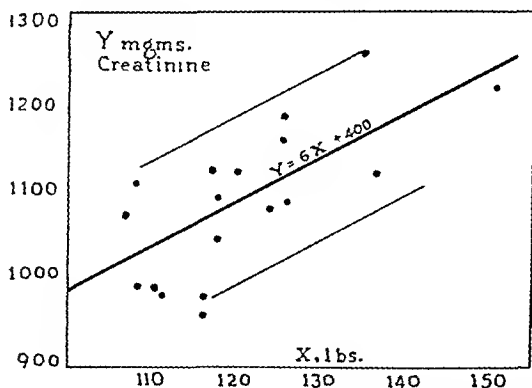


Fig. 2. RELATIONSHIP OF WEIGHT (X), TO CREATININ EXCRETION (Y) in normally-proportioned adult women. Variations of  $\pm 100$  mg. true for 95 per cent of all values.

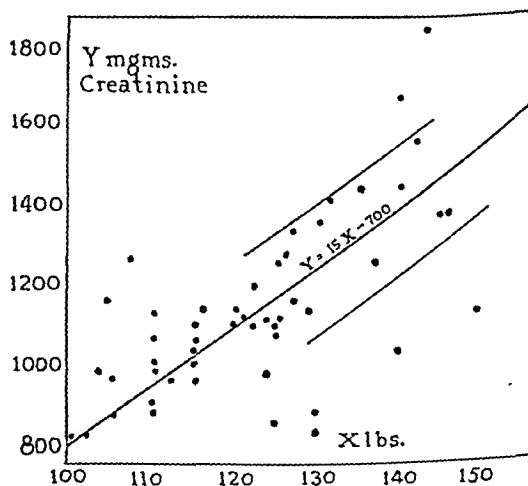


Fig. 3. RELATIONSHIP BETWEEN WILLOUGHBY OPTIMAL WEIGHT ESTIMATION (X) AND CREATININ EXCRETION per 24 hours (Y) in 50 women. Variation of  $\pm 150$  mg. true for 82 per cent of all values.

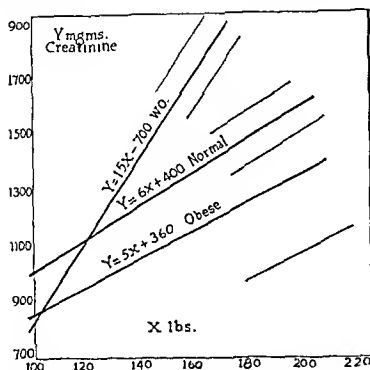


Fig. 4. RELATIONSHIP OF GREATININ EXCRETION PER 24 HOURS (Y) AND WEIGHT (X) IN THE OBESSE AND NORMAL FEMALE. ESTIMATIONS OF RELATIONSHIP TO WILLOUGHBY OPTIMAL (WO) WEIGHT.

creased energy production on the part of the active tissues of the body. It may be recalled that 20 per cent of the obese individuals show variations in basal metabolism outside of the normal range which generally are not to be explained on the basis of thyroid disease. The question may be raised whether the discrepancies are due to variations in muscle mass or its activity, as demonstrated by creatinin excretion. The observation may be made that cases of so-called simple obesity do not form a homogeneous group. Obesity may be part of general bigness; when obesity is associated with large bones and muscle mass, the term macrosomic may be applied. Conversely, the small-boned and poorly muscled person may be termed a microsomic obese individual. Further examination of metabolic data in the light of these observations, i.e., muscle mass and creatinin excretion, is indicated.

#### SUMMARY AND CONCLUSIONS

1. Linear equations expressing the relationship between body weight and creatinin excretion are derived on the basis of a study of 50 adult women.
2. For a known level of creatinin excretion in a given case (whether obese or not) an optimal weight of the patient may be determined by the application of the equation for creatinin-weight relationship established for well-proportioned women. This optimal weight is defined as creatinin-optimal weight.
3. In the absence of an actual laboratory determination, the creatinin excretion and creatinin-optimal weight may be calculated through a conversion equation from the Willoughby optimal weight estimation, based on bone measurements.
4. Creatinin-optimal weight is closely compatible with clinical weight evaluations and offers a physiologic basis for the quantitative expression of the nu-

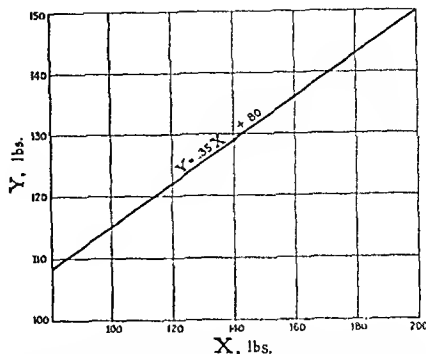


Fig. 5. ESTIMATION OF OPTIMAL WEIGHT. Relation between Willoughby optimal weight (Y) and optimal weight (X) based on creatinin excretion.

tritional state of the adult females.

5. Obese women generally excrete less creatinin than the well-proportioned ones and show more striking variations in the excretion levels from one individual to another at a given weight. These variations are generally in direct agreement with clinical impressions concerning the musculature of the obese.

6. The desirability of clinically differentiating overweight individuals on the basis of muscle mass into the macrosomic and microsomic types is suggested to facilitate further metabolic studies in obesity.

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# Premenstrual Headache Relieved by Estrogen Therapy<sup>1</sup>

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IN THE COURSE of a study of the sex cycle of the human female which is being made in this laboratory, a number of patients have been referred for various disturbances related to menstruation. Of these, one group of 6 patients present a rather constant syndrome, of which the chief complaint is premenstrual headache and a report of the observations seems worth while at this time.

The first patient of this group, *case 1* is an energetic woman in her middle thirties, highstrung, and a participant in a variety of community activities. She complained of severe throbbing headache the onset of which could be expected regularly 6 days premenstrually. The headache persisted with varying intensity until the 2nd or 3rd day of the menstrual flow. During this period of constant headache, the patient experienced fears, chiefly of impending catastrophe, either to herself or to her family. The headaches and fears were of such intensity as to prevent her from carrying on, not merely the variety of social duties to which she was committed, but even the routine household chores which usually she could dispose of in an hour or two. The complaint was of nearly a year's duration at the time when she was referred for study. During the year she had tried to relieve herself by employing one after another of the usual variety of headache remedies ranging from aspirin in heroic doses through the more complicated antidolorous compounds. She had also consulted several physicians and had undergone an extensive physical examination which ruled out the organic lesions most frequently responsible for headaches of such intensity.

Menarche had occurred at 14.5 years of age. The periods had initially been profuse, with 6 days of flow every 26 or 27 days. There was occasional dysmenorrhea. She had married at 26 and had one child 2 years later. Since the birth of the child she had used contraceptives. She had noticed that during the past 2

years the periods had become a little scantier and spaced a little further apart. The flow was now 4 to 5 days every 29 to 30 days. Physical examination revealed no abnormalities.

Because of the association of the headaches with the menstrual period, vaginal smears were made daily and studied. Post-menstrually there was the usual progressive increase in cornification of the vaginal epithelial cells. On the 13th day the change associated with ovulation was noted. Epithelial desquamation and folding of the cells in the smears of the post-ovulative phase, which is characteristic of progesterone and estrogen activity, continued to occur in the normal manner for 7 more days. On the 20th day of the cycle, she reported that on her way to the hospital for the examination she had had serious misgivings that she would have an accident. The vaginal smear on that day consisted of cell types 7-1-8 (1), indicative of an abnormally low hormone level in a woman not yet in the menopause. Headache began in the evening. On the next day the vaginal smear was essentially the same. The patient feared she would be unable to continue her daily visits, for she was usually confined to bed for most of the pre-menstrual week. Since the smears indicated so low a hormone level, it was considered worth while to test the effect of an estrogen supplement. Accordingly, 1 mg. of estradiol dipropionate<sup>2</sup> was given intramuscularly. On the next day she appeared, wearing a new dress and a new smile. She reported that 4 or 5 hours after the injection she had begun to feel elated. The headache faded to a dull heaviness which no longer bothered her. She shopped in the afternoon and visited friends in the evening. The smear consisted of cell types 7-1-(2) (1), indicating a slight elevation in estrogen effect. The estrogen level continued to increase slightly during the next 4 days and then began to diminish gradually. Menses began on the 28th day of the cycle. The patient was free from headache and from phobia during the entire period with no further

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<sup>2</sup> The estradiol dipropionate, Di-Ovocylin, was supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

therapy. In subsequent months, she received varying doses of estrogens, in an attempt to discover the minimal effective dose and the optimal dose. During a vacation, a month without therapy, there was a recurrence of the symptoms, with their usual severity.

The second patient, case 2, was referred by a psychiatrist. Further endocrine study was requested because the results of a general physical and gynecologic examination were negative, and there was a history of progressively scantier menses. Vaginal smears made daily were normal until the 18th day of the cycle. At that time there was a regression of the cell types, with the gradual appearance of cells from the deeper layers of the vaginal mucosa. On the 23rd day of the cycle a few type 8 cells were first noted. Headaches associated with hunger began 2 days later, when the vaginal smear showed 7-8 (1) indicative of an abnormally low hormone level for so young a woman. On the basis of the experience with the previous case, 1 mg of estradiol dipropionate was administered. The next day the patient reported an absence of abnormal hunger, even some revulsion at the smell of food, and a marked reduction in the severity of the headache. The vaginal smears showed progressive cornification up to the time of menstruation which began on the 31st day. The flow was scanty, consisting of but one gush of bright red blood followed by spotting for two days. In the second month the vaginal smears showed essentially the same pattern as before. On the 27th day, 3 days after type 8 cells had first been noted in this cycle, the patient again complained of both headaches and hunger sensations. Twenty gm of glucose was administered intravenously after blood had been drawn for a fasting blood sugar determination. The glucose relieved the hunger sensations only for 30 minutes, and the headache grew progressively more severe. One mg of estradiol dipropionate and 5 mg of progesterone<sup>2</sup> were administered together intramuscularly. The patient reported immediate relief of symptoms, much more complete than when estradiol alone had been given the month before. Indeed, the promptness of response was such as to suggest that the effect of the injection might have been psychic. However, menses began 3 days later with only a slight backache, the flow was more profuse than it had been for several years. It was of 3 days' duration with spotting on the 4th day. In the 3rd month, on the 26th day, she was given a placebo injection intramuscularly. The headache failed to respond to the placebo. The next day, with symptoms increasing in severity, she was given 5 mg of progesterone in oil, intramuscularly, but this without the estradiol was ineffective. She reported an increased severity of the

headache and increased hunger pains. Menses which followed 3 days later resembled that of the preceding month. In subsequent months she has been receiving 0.1 mg of diethylstilbestrol per day during the last two weeks of each cycle. This therapy is more practicable than the estradiol and progesterone injection and serves to control the headache and hunger moderately well. It has made the menses somewhat more profuse than before therapy was instituted. The average duration of flow during the past 3 months has been 2-5 days.

Case 3 is a professional woman, married and in the latter thirties. Like the other patients, she is a nervous, highstrung, active woman trying to do two jobs at once. She was referred as a sterility problem. The vaginal smear pattern was essentially normal, except that the smears of the premenstrual week resembled those of women in menopause. The injection of 0.5 mg of estradiol dipropionate intramuscularly about 1 week premenstrually prevented completely the occurrence of incapacitating headache. Therapy with diethylstilbestrol failed. Since receiving therapy she can carry on her work more efficiently and effectively than before. This therapy has been continued for 6 months.

Case 4 is precisely like case 3 except that the patient was referred specifically because of premenstrual headaches, and the headache has been successfully controlled for 5 months, by a single injection of 0.5 mg of estradiol dipropionate given a week premenstrually.

Case 5 is an unmarried professional woman, 29 years old. Menarche had occurred at 14.5 years. Her next menstrual period came when she was 16 years old. The onset of the premenstrual headaches dated from about age 21, when she had had an episode of serious menorrhagia requiring surgical intervention, and transfusion. This never recurred. About 8 years ago, on the day preceding menses, she had severe left-sided headaches beginning over the occiput and radiating into the left eye. At times she felt 'half blinded.' During the last year she had had to spend 2 or 3 days of each month in bed, and had been given morphine on several occasions to control the pain. When menstrual flow began the headache disappeared. Vaginal smear study revealed that ovulation occurred on the 7th day of the cycle. There was a normal post-ovulatory cell pattern in the smears following the usual course for about 12 days. Fragmented cells, but no red blood cells, then became the predominant characteristic of the vaginal smear picture, indicating a very low hormone level. The vaginal smear remained essentially unchanged until menses occurred on the 29th day. In the second cycle, diethyl-

<sup>2</sup> Progesterone (Lycotycin) was supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

stilbestrol,<sup>4</sup> 0.5 mg. per day, was given starting about 10 days before the expected menses. The patient experienced transient nausea on the second day of medication. Headache did not occur. The vaginal smear studies revealed the effect of the estrogen dosage. The epithelial cells were types 2-7-3(1). Menstruation occurred a day sooner than expected, on the 17th post-ovulative day, the 27th day of this cycle. The flow was somewhat more profuse than usual, but otherwise was not remarkable. This schedule of therapy has been used for 4 months without further recurrence of headaches.

Case 6 was seen in the course of only 2 months. She had had very thorough examinations by competent physicians elsewhere. She is a woman in her early forties, supporting herself and her family. For the past 5 years she had noticed that the menses had become more scanty. Premenstrual headaches had been growing progressively more severe until they threatened to impair, if not, disrupt her ability to earn a living. She was first seen on the first day of a headache, the 22nd day of that cycle. The vaginal smear on that day was typically pre-menopause containing cell types 2-7-8(1). She was given 1 mg. of estradiol dipropionate intramuscularly and was asked to report results a week later. She reported that the injection aborted the mild headache and that during the premenstrual week she felt better than she had 'for 10 years before.' In the second cycle she was given diethylstilbestrol, 0.1 mg. a day, starting on the 16th day of the cycle. This medication controlled the severity of the headache but failed to prevent it completely. Further experiments with timing and dosage will be required in order to find the optimal therapy for this patient.

#### DISCUSSION

The need for estrogen in 6 relatively young women with active ovarian function suggests that gonad hormone production may fall below physiologic requirements, despite maintenance of menstrual function. This observation should be considered together with the evidences that continued ovarian function may persist even after cessation of menses. Thus, just as the period of adolescence is protracted, and the menarche by no means represents complete maturity

of reproductive capacity (2, 3), so the loss of reproductive capacity must be considered a gradual process. In most women, the approaching menopause is heralded by scantier menses and longer intermenstrual intervals. In a few women, 'menopausal' symptoms may develop despite little change in the character of the menses. It is probable, in the light of our psychosomatic investigation (4, 5) that those women whose environment demands severe nervous integration and coordination will suffer most from lack of estrogen. This hypothesis fits well with the fact that all 6 of these patients are active, highstrung, nervous women engaged in work outside the home.

The 6 cases reveal certain similarities, a), severe, incapacitating premenstrual headache; b), nervous, highstrung, active women; c), childbearing age; d) vaginal smears consisting predominantly of fragmented cells (type 7) and cells from deep layers of the mucosa (types 1 and 8); i.e., the premenstrual phase presents smears indicative of a relatively atrophic vaginal mucosa and suggests the existence of an abnormally low gonad hormone production; such smears are never found in young adult women unless there is vaginitis; e) prompt amelioration of the symptoms occurring with moderate estrogen dosage; f) dosage and timing of the therapy seem to require individual adjustment, although in the cases so far studied, 1 mg. of estradiol dipropionate intramuscularly about a week before the onset of menses is adequate, if not optimal.

Many more patients suffering from severe premenstrual headache should be carefully studied to determine the validity of the syndrome. The vaginal smear technique is a useful and practical diagnostic aid for this purpose.

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<sup>4</sup> The diethylstilbestrol was supplied by Dr. E. G. Upjohn, of The Upjohn Co., Kalamazoo, Mich.



# Ethinyl Estradiol: A Clinical Evaluation

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THE QUEST for an orally effective estrogen has occupied the attention of chemists for the past decade. This search has been greatly accelerated during the past few years, and remarkable results have been obtained, particularly in the production of non-steroid compounds that possess great estrogenic activity. Of this group, diethylstilbestrol is very potent and does not lose its effectiveness on oral administration. The natural estrogens, when taken orally, are comparatively ineffective. This has been shown to be due to inactivation by the liver (1). Hohlweg and Imhoffen (2) prepared ethinyl estradiol which, although a natural estrogen, is active on oral administration. They report that it is 15 to 20 times as effective as estradiol when taken by mouth. The presence of the ethinyl radical probably protects the estrogenic activity of the compound, either from destruction in the gastro-intestinal tract or from inactivation by the liver. Preliminary investigation of the activity of this compound in castrated female rats, by the method used previously in the study of estrone and estradiol, has shown that in comparable amounts, the liver is not able to inactivate ethinyl estradiol (3). There have been very few reports on the clinical use of ethinyl estradiol (4); the following is an analysis of the results observed in 33 menopausal women.

## METHOD OF INVESTIGATION

Of the 33 cases studied, 20 had undergone a natural and 13 an artificial menopause. All complained of the usual symptoms: flushes, sweats, headaches, dizziness, numbness of the extremities, arthralgias, excessive fatigue, insomnia and nervousness. In both groups the severity of the symptoms varied considerably, and in general the surgical castrates presented the most severe symptoms. It was possible to study many of the patients for periods as long as 2 years.

Minimal doses of the ethinyl estradiol<sup>1</sup> were used in all instances. The preparation was originally sup-

plied in tablets containing 0.15 mg. and later, as tablets containing 0.05 mg. When ethinyl estradiol was first employed the majority of patients was given 0.15 mg. daily for a period of 14 to 21 days, and the dosage was then decreased to 0.15 mg. every other day. In a few instances 0.30 mg. was the initial daily dose and this was gradually decreased after 7 to 14 days. It was found that this latter large dosage alleviated symptoms within 4 or 5 days. Most of the symptoms were completely relieved in 7 to 10 days. Later it was found that if 0.05 mg. was taken 2 or 3 times daily and the dosage slowly decreased to once a day the symptoms were controlled. Those women who were passing through a natural menopause, as a rule, required less medication, and frequently could stop using the drug for several weeks at a time. With the reappearance of symptoms the patients returned for further therapy.

Our evaluation of the therapeutic effectiveness of this new compound in the treatment of the diverse symptoms of the menopause is based mainly on its ability to control the symptoms; its estrogenic activity is of secondary importance. For this information we were directly dependent on the reactions of the patients to the drug, and we attempted to interpret these as objectively as possible. The major symptoms, the flushes, sweats, headaches and dizziness, in all but 4 instances, disappeared in 7 to 10 days and remained in abeyance as long as administration of the drug was continued. In two cases there was but moderate control of symptoms. When an occasional flush occurred the patients stated it was mild and tolerable. There was a marked improvement in the general well being of all these patients. It was noted that with symptoms well controlled on adequate therapy that a physical or psychic upset would induce a recurrence of flushes and sweats.

*Vaginal smears.* Smears stained by the method of

<sup>1</sup> The ethinyl estradiol used in this study was supplied through the courtesy of Dr. William R. Bond of the Schering Corp., Bloomfield, N. J.

Salmon and Frank (5) were made at regular and frequent intervals on all cases. The changes in the smears did not always parallel the course of clinical improvement. A cornification of the vaginal epithelium is generally expected to accompany symptomatic relief, but often the cells in the smear remained the same in appearance or changed slightly, and in many instances the smear continued to show

yielded merely a mixture of blood and mucus. After the treatment with ethinyl estradiol was well under way endometrial tissue could be obtained more easily from these patients. These biopsies in most instances showed the endometrium in the proliferative stage, and some specimens revealed a marked hyperplasia with dilated and cystic glands. The histologic picture was characteristic and concurs in all respects with

TABLE I. DATA ON MENOPAUSAL PATIENTS TREATED WITH ETHINYL ESTRADIOL

| Case and Name | Age, yr | Occurrence of Last Menses             | Type of Menopause | Period of Treatment | Type of Endometrium                                   | Bleeding During Treatment   | Total Dosage mg |
|---------------|---------|---------------------------------------|-------------------|---------------------|---|---|-----------------|
| 1 Mrs S F     | 45      | 3½ years ago                          | Natural           | 12/28/40-6/15/42    | 11/8/41, Cystic hyperplasia<br>2/26/42, Proliferative | Intermittent episodes of bleeding finally resulting in curettage on 2/28/42 | 33 0            |
| 2, Mrs A P    | 44      | Regularly recur every 5-6 weeks       | Natural           | 12/28/40-4/10/41    |   | None  | 7 2             |
| 3, Mrs P V    | 45      | 3 years ago                           | Natural           | 8/3/40-6/7/41       |   | None  | 9 15            |
| 4, Mrs T T    | 57      | 2½ years ago                          | Natural           | 1/4/41-2/18/41      |   | None  | 6 75            |
| 5, Mrs E S    | 48      | Regular recurrence every 28 days      | Natural           | 8/31/40-7/9/42      | 9/14/40 No tissue obtainable                          | Slight spotting   | 14 1            |
| 6, Mrs A G    | 48      | 3 months ago                          | Natural           | 1/25/41-3/22/41     | 1/25/41, Secretory                                    | None  | 6 45            |
| 7, Mrs A S    | 57      | 10 months ago                         | Natural           | 11/2/40 3/1/41      | 11/2/40 No tissue obtainable                          | None  | 8 25            |
| 8 Mrs A G     | 58      | 8 years ago                           | Surgical          | 2/15/41-4/15/41     |   | None  | 6 15            |
| 9, Mrs R P    | 39      | 5 years ago                           | Surgical          | 8/3/40-2/27/41      |   | None  | 9 75            |
| 10 Mrs A B    | 33      | 12/10/40                              | Surgical          | 1/25/41-7/9/42      | 8/14/41, Proliferative<br>9/15/41, Proliferative      | Fairly regular periods with occasional episodes of prolonged bleeding       | 49 05           |
| 11, Mrs P K   | 42      | Regular recurrence every 30 days      | Natural           | 2/27/41-6/12/41     |   | Slight spotting   | 7 05            |
| 12, Mrs M B   | 43      | 1 year ago                            | Surgical          | 12/21/40-5/3/41     |   | None  | 12 30           |
| 13, Mrs E F   | 52      | May, 1940                             | Natural           | 10/5/40-7/16/42     | 10/5/40, Resting<br>8/14/41, Secretory phase          | Fairly regular periods about every 2 months                                 | 30 15           |
| 14, Mrs S K   | 43      | Regular recurrence every 26 days      | Natural           | 4/10/41-5/24/41     |   | None  | 5 1             |
| 15, Mrs B F   | 51      | 3 months ago                          | Natural           | 11/6/40-10/11/41    |   | None  | 12 3            |
| 16, Mrs E B   | 47      | March, 1940                           | Surgical          | 12/28/40-7/9/42     |   | None  | 38 4            |
| 17, Mrs B G   | 42      | December, 1940                        | Natural           | 2/8/41-6/26/41      | 2/18/41, Proliferative                                | None  | 6 9             |
| 18, Mrs T P   | 49      | 1937                                  | Surgical          | 8/3/40-8/14/41      |   | None  | 8 1             |
| 19, Mrs S B   | 50      | April, 1941                           | Natural           | 4/27/41-6/25/42     | 7/10/41, Proliferative                                | Spotting and slight bleeding at irregular intervals                         | 12 6            |
| 20, Mrs L N   | 35      | April, 1941                           | Surgical          | 8/31/40-9/25/41     | 9/5/41, Proliferative<br>9/18/41, Proliferative       | Profuse, prolonged bleeding   | 6 75            |
| 21, Mrs B K   | 46      | April, 1941                           | Natural           | 12/18/41-8/27/42    |   | Profuse, intermittent bleeding  | 8 4             |
| 22, Mrs A F   | 45      | February, 1942                        | Surgical          | 4/9/42-8/27/42      |   | None  | 12 9            |
| 23, Mrs R B   | 43      | December, 1941                        | λ ray             | 3/7/42-5/28/42      | 3/7/42, No tissue obtainable                          | None  | 13 5            |
| 24, Mrs I B   | 42      | December, 1941                        | Surgical          | 3/26/42-8/20/42     |   | None  | 8 4             |
| 25, Mrs B G   | 45      | Irregularly recur every 6-8 weeks     | Natural           | 5/12/41-6/8/42      | 3/27/42, Proliferative                                | None  | 12 6            |
| 26, Mrs E B H | 52      | Regular recurrence every 28 days      | Natural           | 9/18/41-8/27/42     |   | Slightly prolonged period   | 18 9            |
| 27, Mrs J M   | 40      | Irregularly recur every 6-8 weeks     | Surgical          | 2/4/41-6/18/42      | 6/13/41, Proliferative                                | Profuse, intermittent bleeding  | 21 3            |
| 28, Mrs J K S | 40      | May, 1936                             | Surgical          | 10/24/41-1/17/42    |   | None  | 8 4             |
| 29, Mrs U R   | 52      | Regular recurrence every 5 weeks      | Natural           | 8/7/41-5/21/42      |   | Slight spotting   | 12 3            |
| 30, Miss G R  | 53      | 5 years ago                           | Natural           | 9/9/41-4/20/42      |   | None  | 11 4            |
| 31, Mrs M S   | 45      | Irregularly recur at 28 day intervals | Natural           | 8/10/40 8/17/42     | 9/15/41, Proliferative                                | Profuse, intermittent bleeding  | 25 2            |
| 2, Mrs C H    | 45      | 4 years ago                           | λ ray             | 7/2/41-7/30/42      |   | Slight bleeding   | 18 7            |
| 3, Mrs J D    | 39      | 6 years ago                           | Surgical          | 9/12/40-7/21/42     |   | None  | 38 4            |

atrophy cells. It is assumed that if large doses of ethinyl estradiol were given it would have been possible to convert the atrophic vaginal mucosa to the mature type, however our object was to obtain symptomatic relief.

*Endometrial biopsies.* Whenever possible biopsies were obtained from the patients in the Outpatient Department in order to study the endometrial changes. Obtaining biopsy specimens without an anesthetic is a painful procedure in some instances. Nevertheless it was done as often as possible in suitable cases, especially in multiparas on whom the cervical canal was easily dilated. We have found it difficult to obtain satisfactory endometrial tissue in the menopausal patient who has not menstruated for several months or years. Repeated attempts at biopsy

reports in previous papers on the effects of other estrogens on the endometrium.

Several undesirable effects were noted during the period of treatment which are worthy of discussion. The first two were expected and their appearance caused no surprise.

*Bleeding.* The presence of proliferative endometrium in many of the cases was accompanied by slight or marked bleeding in 5 instances. Several patients in this series who had not menstruated for years were both alarmed and surprised when flowing again. Others have had marked bleeding over a period of 10 days which subsided to a slight flow lasting for 7 to 14 days. In one instance bleeding continued for 35 days and was accompanied by severe cramps and lower abdominal pain. It was necessary to admit this

patient to the hospital for a curettage. The endometrium was hyperplastic and its removal was followed by a cessation of the bleeding.

Bleeding was reported by the patients during the period when they were taking the drug. In several ovariectomized patients, in whom the uterus was still present, the bleeding was almost cyclic in its recurrence and character during treatment. Withdrawal bleeding occurred in one instance. No attempt was made to treat this bleeding with other agents.

*Leukorrheal discharge.* Several patients complained

cases which were especially interesting are reviewed briefly.

#### CASE REPORTS

*Case 1. Mrs. S.F.,* age 45 years. This patient was an extremely emotional, nervous woman who had had several major operations. She had been a chronic invalid for years. She complained of flushes, sweats, insomnia, nervousness, headache, dizziness and amenorrhea of  $3\frac{1}{2}$  years duration. Her response to ethinyl estradiol was dramatic, with a prompt disappearance of the symptoms within 7 days.



Fig. 1. Fragments of endometrium composed of uniformly small glands widely spaced in an edematous stroma, case 1.

Fig. 2. Endometrium, showing extreme variation in size and shape of glands with some undergoing cystic dilatation; case 1.

of the appearance of a white discharge. This symptom was apparently due to the increased maturation and cornification of the vaginal epithelium as a direct result of the specific treatment.

*Headaches.* Three patients suffered from severe headaches which can be attributed to the effects of the drug. In two instances the headaches subsided while the treatment was continued; one lasting 14 days, the other 3 days. In the third instance it was necessary to discontinue the use of the compound after 2 weeks during which time the headaches persisted.

*Nausea and vomiting.* The patients were under constant observation for these and related symptoms which commonly occur during diethylstilbestrol therapy; however, they did not manifest themselves.

Most of the patients studied were able to take ethinyl estradiol with excellent results and without unusual symptoms or side effects being noted. Two

Beginning on Dec. 28, 1940, a dosage of 0.30 mg of ethinyl estradiol daily was given. This was reduced to 0.15 mg. after 10 days. Catamenia lasting 8 days began on Feb. 3, 1941. This was the first period of flow in  $3\frac{1}{2}$  years. On May 17 flowing appeared and lasted for 1 day. The patient had been feeling unusually well. On August 20 flow began and continued for 14 days. The patient had been enjoying excellent health, was less nervous and seeking employment. On October 18 she reported there had been no bleeding since September 3. She was enthusiastic about the way she was feeling, and she was employed at this time. The normal resting endometrium shown in figure 1 was obtained from this patient. On November 13 a slight flow began lasting for 4 days. On December 3, twenty-one days later, a moderate continuous flow lasting for 9 days began. Six weeks later, on Jan. 13, 1942, a 4-day catamenia began which was accompanied by moderately severe cramps. Figure 2 shows the cystic hyperplasia of the endometrium in this case. On Feb. 12, 1942, the patient reported a continual flow accompanied by lower abdominal pain. By February 28 this had become a profuse bleeding

and she was hospitalized for curettement. This was performed under gas anesthesia and she was discharged after 48 hours. On April 8, 1942, she reported there had been no bleeding since her discharge from the hospital.

**Case 10, Mrs. A.B.,** age 33 years. The patient is known to have had diabetes since 1930. She had had two abdominal operations, the first in April, 1940, at which time the right tube and a cystic ovary were removed. In December of the same year a second operation was performed for an ectopic pregnancy which was complicated by a massive hemorrhage. Within a week following the second operation she complained of marked flushes and sweats. She was given 0.30 mg. of ethinyl estradiol daily, beginning on Jan. 25, 1941, and she has continued to take it in varying dosages until the present time. The response to treatment with ethinyl estradiol has been gratifying. The flushes and sweats disappeared and she stated that she felt like her usual self. Her weight increased from 161 to 177 lb. During January and February of 1942 the average dosage of ethinyl estradiol was 0.05 mg. per day.

The cycles of bleeding which have recurred since the second operation are of interest in view of the fact that both tubes and ovaries had been removed. The first episode of flowing after initiation of treatment on January 25, was on March 2. The amount was scanty and lasted but 1 day. A normal flow of moderate amount lasting for 3 days began on March 29, 28 days after the previous 1-day period. On June 7 a 4-day period began after an interval of 70 days. The flow was heavy and associated with lower abdominal cramps. After an interval of 24 days a 3-day period began on July 11, which was followed in turn by an interval of 9 days; a scant flow lasting 2 days began on July 19. Sixteen days later, on August 4, a scant flow started which lasted for 3 days. A scant flow, lasting for 1 day, appeared on August 24, after a 21-day interval. Thirty-four days later, on September 27 there was a moderate flow of 4 days' duration. On October 20 spotting appeared for 1 day after an interval of 24 days. Sixty-six days later, December 24, a scanty flow associated with a few crampy pains appeared and lasted for 2 days. On Feb. 10, 1942, a moderate flow of 5 days' duration began after an interval of 49 days.

#### DISCUSSION

During the past few years the development of oral estrogenic therapy has provided an economical method for treating menopausal patients. This has become increasingly important since it is obvious that estrogenic therapy is substitution therapy and often must be continued for months or years. Numerous preparations, of which diethylstilbestrol and its derivatives are the most effective, have been tried. None has proved entirely satisfactory owing either to lack of potency on oral administration, or to various untoward side effects. The use of diethylstilbestrol, the most potent oral compound available, which singularly enough is not a steroid, is often attended

by nausea and vomiting and this militates against its use in many cases (6). The development of an orally effective steroid estrogen, ethinyl estradiol, which in our hands has shown practically no toxic symptoms, is a welcome advance. Little is known concerning the metabolism of diethylstilbestrol or the mechanism of its ultimate disposal by the body, except that it may not be inactivated by the liver in the manner estrone and estradiol are (3). Estradiol on the other hand, is a natural product of glandular metabolism, and its synthetic ester, ethinyl estradiol, is more likely to be assimilated and catabolized by the body with fewer untoward reactions. The recent observations on the control of the inactivating function of the liver by vitamin B complex (7, 8), suggests that the minor side effects related to the administration of this compound may be relieved by giving the vitamin with it.

#### SUMMARY AND CONCLUSIONS

Ethinyl estradiol was administered orally to a group of 33 menopausal women. The dosage varied from 0.05 to 0.15 mg., given one to 3 times daily. Excellent control of symptoms occurred in 27 cases, moderate control in 2 cases, and in only 4 cases was the drug ineffective. Vaginal smears and endometrial biopsies in most of the cases showed changes compatible with estrogenic activity after variable periods of therapy. Vaginal bleeding during therapy appeared in 7 cases; withdrawal bleeding occurred on cessation of therapy in one case. During treatment 3 patients complained of headaches; in one it was sufficiently severe to necessitate discontinuing treatment, in the other two the headaches disappeared. Nausea and vomiting did not occur. This new oral steroid estrogen, ethinyl estradiol, has shown great effectiveness in controlling the symptoms of the menopause. The toxic manifestations that have been described with the nonsteroid oral estrogens did not occur.

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# Male Hypogonadism: Effect of Treatment on Genital Growth and Maturity

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METHYL TESTOSTERONE is a potent androgen which is orally effective. Clinical experience with substitution therapy (1-31) in male hypogonadism has produced generally satisfactory, but not always completely successful results. The technique of medication, criteria for dosage and the possibility of producing side effects require further elaboration. A comparison of the results reported with those of a new, and previously untried, concentrated preparation of testosterone propionate injection is of interest. Finally, variations in the initial clinical picture of the hypogonad male and of his response to treatment deserve further emphasis in order to facilitate a more accurate prognosis in a given case.

## MATERIAL, MEDICATION AND METHOD

This report concerns the effect of male hormone administration in 9 hypogonad males over 18 years of age, 8 of whom also displayed a marked hypogonadism. The subjects have been observed over a period of 4 months to 2 1/2 years. All were examined from a systemic and metabolic point of view, including routine laboratory studies of the urine and blood for formed elements and serologic reaction, determination of the basal metabolic rate, serum cholesterol, calcium, phosphorus and sugar tolerance as well as roentgen visualization of the skull, sella turcica and epiphyseal maturity. The clinical study generally followed lines already previously described. Brief condensations of pertinent information regarding initial findings, medication and results are tabulated in table 1.

Methyl testosterone,<sup>1</sup> containing 10 mg of the active substance per tablet was given orally, with a little water, once daily, at bedtime. Abstinence from food for the preceding 4 hours appeared to promote the action of the drug, while administration at the time of retirement provided an optimal period of body

relaxation to gauge the maximal stimulation overnight and on arising. The occurrence of nocturnal or morning erections varying in frequency from once or more in 24 hours in the early phases of treatment to several times per week later, served as the criterion for the adequacy of the dosage. An average of 10 to 30 mg. daily appeared to be sufficient for this demonstration of physiologic effectiveness.

A testosterone propionate injection<sup>1</sup> containing 25 mg. of the active substance per gm. of the base was later substituted for oral therapy over a period of 3 months in 4 of the cases of hypogonadism and hypogonadism. The ointment was applied at bedtime to the lower abdomen or inner aspects of the thigh and rubbed thoroughly into the surface without preliminary preparation of the skin. In some instances the ointment was also applied directly to the penis or to the areas of potential hairgrowth in an effort to promote local effects. A daily dosage of 12 1/2 mg. of androgen percutaneously seemed comparable in its effectiveness to twice the amount of methyl testosterone orally as judged by the criterion described. Percutaneous application was no more troublesome than the oral route.

Progress in the stimulation of penile growth was determined by the increase in the length of the organ both in the relaxed and erectile state. Measurement of the relaxed organ did not appear to be entirely satisfactory because of its retractile properties depending upon the tone of the smooth muscle, the autonomic nervous system and temperature, which vary with constitutional differences between individuals, as well as in a given individual from time to time. A more constant and dependable figure was obtained during erection. This method of measurement has the additional merit of including an index of total penile vascular capacity. Normal individuals differ considerably in this genital 'coefficient of expansion.' The short and stocky type may attain an erection 4 to 5 times that of the initially short penile contractile length, while in a slender-boned, leptosome with pendulous genitalia, the increment may be less pronounced. The relaxed length from base to

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<sup>1</sup> The methyl testosterone and the testosterone propionate injection were supplied by Dr. E. Oppenheimer, Dr. R. McBrayer and Mr. L. H. Neil of Ciba Pharmaceutical Products, Inc., Summit, N. J.



tip of the glans was recorded by the physician while the spontaneous erectile length, usually available before the first morning voiding, was similarly measured

by the patient. Although open to the criticism that the latter process necessitated the acceptance of data collected by the patient and that, therefore, it is sub-

TABLE 1 CLINICAL DATA IN HYPOGONAD CASES

| Case No.  | Clinical History   | Medication  | Months of Observation | Wt., lb. | Ht., in. | Genital Length, in. |          | Genital (Pubic Hair) Maturity | Observation  | Comment   |
|---|--|---|-----------------------|----------|----------|---------------------|----------|-------------------------------|--|---|
|   |  |   |                       |          |          | Re-tracted          | Erectile |                               |  |   |
| 1, P.W.<br>age 19 yr<br>Observation period 21 mo  | Cryptorchid and hypogonital at 10. Few pubic hairs at 16. Severe fatigability. Impulse poorly sustained. Emotional lability. Excellent intelligence. Sexuosity toward females. No contacts. College student. Configuration fleshy with long extremities. Autonomic instability. Parents average build. No endocrine disease. | None  | Initial               | 140      | 66.4     | 0.5                 |          | trace                         | Fig 1, A Left testicle in external ring. Surgery one year later, fibrous tissue.                               | Hypogonad. Libido and neurovascular irritability well maintained throughout with treatment. Genital growth excellent up to full pubic hair thickness, none following skeletal response with maturation. |
|   |  | Testosterone propionate injection, 14 mg daily        | 2                     |          |          | 1.5                 | 2.5      | 1+                            |  |   |
|   |  | Methyl testosterone 40 mg                             | 3                     |          | 67.5     | 2.5                 | 3.5      | 2+                            | Fig 1, B Voice deepening   |   |
|   |  | None  | 3                     |          | 68.4     | 3.0                 | 4.5      | 4+                            | Fig 1, C Voice deep. Severe acne   |   |
|   |  | 20 mg   | 10                    | 157      | 69.6     | 3.0                 | 4.5      | 4+                            | Axillary hair. Broadening of bones   |   |
|   |  | Testosterone propionate injection, 25 mg daily        | 4                     | 155      | 71.0     | 3.0                 | 4.5      | 4+                            | Epiphyses open. No facial hair   |   |
| 2, G.R.,<br>age 19 yr<br>Observation period 27 mo | Cryptorchid and hypogonital at 14. Minimal pubic hair development, 20-25 yr. Tall, big boned, progressive obesity. Hard working, ambitious, even tempered. Good intelligence. Machinist. Normal sex uousity, but no contacts. Parents and 5 brothers tall and big boned.   | None  | Initial               | 263      | 70.0     | 0.5                 |          | 1+                            | Fig 2, A Both testes pea-size, soft, insensitive. No sperm   | Hypogonad. Libido and neurovascular irritability of penis well maintained with treatment. Genital growth good up to almost full pubic hair thickness, none since.                                       |
|   |  | Testosterone propionate injection, 25 mg 3x weekly    | 4                     |          |          | 2.5                 | 4.5      | 2+                            | Fig 2, B Fewer erections   |   |
|   |  | Chorionic gonadotropin 1,000 i.u. 3x weekly injection | 4                     |          |          | 2.5                 | 4.5      | 2+                            | Fig 2, B Fewer erections   |   |
|   |  | Methyl testosterone 50-100 mg orally                  | 7                     | 208      | 70.0     | 3.0                 | 5        | 3+                            | Fig 2, C Voice deep. Axillary hair appearing. No facial hair. Sex interest. Dancing. Weight loss through diet. |   |
|   |  | 30 mg   | 9                     | 210      | 70.0     | 3.0                 | 5        | 3+                            |  |   |
|   |  | Testosterone propionate injection 12.5 mg             | 3                     | 201      | 70.0     | 3.0                 | 5        | 3+                            | Scattered chin hairs   |   |
| 3, J.H.,<br>age 18 yr<br>Observation period 21 mo | Cryptorchid and no pubic hair at 15. Completely atrophic testes removed surgically. Tall, slender-boned, athletic. Good impulse, even tempered, good intelligence. Good student. Normal sex uousity, but no contacts. Parents normal, tall.  | None  | Initial               | 120      | 68.9     | 1.0                 |          | 0                             | Fig 3, A, Testes not present   | Hypogonad (castrate). Libido and neurovascular irritability well maintained with treatment. Genital growth good up to almost full pubic hair thickness, none since. Good skeletal and muscle response.  |
|   |  | Chorionic gonadotropin 1,000 i.u. 3x weekly injection | 3                     | 121      | 69.0     | 1.0                 | 1.5      | 0                             |  |   |
|   |  | Methyl testosterone, 40 mg                            | 3                     | 146      | 70.0     | 3.0                 | 4        | 1+                            | Fig 3, B Voice breaking  |   |
|   |  | 30 mg   | 12                    | 147      | 72.3     | 3.0                 | 4.5      | 3+                            | Fig 3, C Voice deep. Moderate axillary hair but none on face.  |   |
|   |  | Testosterone propionate injection, 12.5 mg            | 3                     | 148      | 72.2     | 3.5                 | 5        | 3+                            | Epiphyses open   |   |
| 4, E.S.,<br>age 18 yr<br>Observation period 26 mo | Genital hypoplasia through childhood. Pubic hair at 15. Weak to no sex interest. Tall, broad-boned. Weak in impulse, sensitive, irritable. Dull intelligence, retarded in school. Parents tall, broad-boned. Mother tall, hypogonad, hysterical psychopath.  | None  | Initial               | 214      | 67.9     | 1.5                 | 3        | 3+                            | Testes bean size   | Hypogonadism and some hypogonadism, mild. Libido and neurovascular irritability good with treatment. No genital growth response with beginning of therapy near full pubic hair thickness.               |
|   |  | None  | 14                    | 197      | 68.7     | 1.5                 | 3        | 4+                            | Testes olive size. Normal sperm  |   |
|   |  | Methyl testosterone, 40 mg                            | 6                     | 204      | 69.9     | 1.5                 | 4        | 4+                            |  |   |
|   |  | 20 mg   | 3                     | 210      | 70.5     | 1.5                 | 4        | 4+                            | Fig 4 Voice now deep. Some facial hirsutism. Testes firm. Interest in opposite sex.                            |   |
|   |  | Testosterone propionate injection, 12.5 mg            | 4                     | 215      | 70.0     | 1.5                 | 4        | 4+                            | Testes olive size. Normal sperm  |   |

TABLE I. CLINICAL DATA IN HYPOGONAD CASES—Continued

| Case No.  | Clinical History  | Medication   | Months of Observation | Wt. lb. | Ht. in. | Genital Length in | Re. lax | Erec. tile | Genital (Pubic Hair) Matur. st.       | Observation  | Comment   |
|---|---|--|-----------------------|---------|---------|-------------------|---------|------------|---------------------------------------|--|---|
| 5 R.M.<br>age 20 yr<br>Observation period 20 mo | Cryptorchid at 12 Rt. testicle rudimentary in scrotum at 15 with first appearance of pubic hair Broad boned long extremities wide pelvic bones Ambitious sensitive mood swings to mild depression excellent intelligence College student Normal sex interest toward females and trial experience Parents normal   | None   | Initial               | 165     | 65 0    | 0 5               | 1 5     | 3+         | Rt. testicle only palpable, bean size | No enlargement of testis which softened Axillary hair present Voice breaking   | Hypogonad. No genital growth response with beginning of therapy near full pubic hair thickness  |
|   |   | Chronic gonadotropin 1000 i.u. 3X weekly injection | 5                     |         |         | 1 0               | 1 5     | 4+         |                                       |  |   |
|   |   | Testosterone propionate injection 25 mg 3X weekly  | 12                    | 168     | 66 2    | 1 0               | 2 5     | 4+         |                                       | Voice deep Shaves once per week No spermatozoa   |   |
|   |   | Methyl testosterone 30 mg                          | 3                     |         |         | 1 0               | 2       | 4+         |                                       | No further change Fig. 5   |   |
| 6 J.B.<br>age 20 yr<br>Observation period 4 mo  | Pubic hair first at 15 Testes small barely palpable Normal athletic configuration Progressive body hair growth Impulse life work Ambitious winsome temperamental Ego sensitive with marked compensation Dull average intelligence Interest in opposite sex social only Masturbation Parents normal leptosomes     | None   | Initial               | 140     | 72 0    | 1 0               | 4       | 4+         |                                       | Testes soft per testis bean size No spermatozoa Pronounced breast size Shaves daily Voice normal   | Hypogonad. No genital growth response with beginning of therapy after full pubic hair thickening  |
|   |   | Methyl testosterone 30 mg                          | 4                     | 143     | 72 0    | 1 0               | 4       | 4+         |                                       | Fig. 6 Testes soft rudimentary No change Increase in libido aggressiveness and optimism  |   |
| 7 A.W.<br>age 28 yr<br>Observation period 4 mo  | Cryptorchid on rt. Testes small in scrotum at 14 with first appearance of pubic hair Tall broad boned with progressive obesity especially abdominal and chest Marked gynecomastia Impulse poor minor depressions good intelligence Interest in opposite sex but superficially consistently Salesman Parents obese | None   | Initial               | 160     | 67 4    | 1 0               | 2       | 3+         |                                       | Left testicle per testis soft Erect hair present Shaves once per week Chest hair growth Prominent gynecomastia Androgenetic ratio in urine low           | Hypogonad with secondary (compensatory?) adrenogenital syndrome No genital growth response with beginning of therapy near time of full pubic hair thickness |
|   |   | Methyl testosterone 40 mg                          | 4                     | 265     | 67 4    | 1 0               | 2       | 3+         |                                       | No change except increase in libido and penile neurovascular irritability Masturbation   |   |
| 8 P.H.<br>age 31 yr<br>Observation period 4 mo  | Pubic hair genital size and testes normal at 15 Never developed axillary hair and only slight facial hair Massive intracapsular pituitary tumor removed at age of 27 Radiation therapy later Complete loss of libido Divorce Good energy intelligence and normal skeletal build Graduate student                  | None   | Initial               | 165     | 68 7    | 2 5               | 4 5     | 2+         |                                       | Testes olive size firm Shaves 2X weekly No axillary hair 17 ketosteroids to 1 mg Gonadotropin 0 Sella turcica 4X6 cm                                     | Hypogonad secondary to pituitary deficiency Genital maturation not improved with male hormone Some genital growth   |
|   |   | Methyl testosterone 20 mg                          | 4                     | 165     | 68 6    | 3 0               | 5       | 2+         |                                       | No change in facial or pubic hair system Libido and neurovascular irritability of penis normal with treatment  |   |
| 9 E.F.<br>age 40 yr<br>Observation period 6 mo  | Pubic hair first at 15 Testes normal Typhoid fever Facial hair never did grow well Normal body build in skeletal and fat distribution Pituitary infarction at 37 Add son a disease with crises Response to dexamethasone Pituitary myx edema (blood iodine 200) and hypogonadism Loss of libido                   | None   | Initial               | 125     | 65      | 2 0               | 3 5     | 2+         |                                       | Testes olive size Soft Shaves once per week Voice normal Severe secondary menorrhea  | Hypogonad secondary to pituitary deficiency Pituitary myx edema and adrenal cortical deficiency Genital maturation not improved with male hormone           |
|   |   | Methyl testosterone 5 mg                           | 4                     | 125     | 65      | 3 0               | 4       | 2+         |                                       | Response in libido and neurovascular irritability normal with treatment Some genital growth Troublesome priapism if dose of male hormone raised to 10 mg |   |

ject to mistakes or exaggeration, the facility of the procedure and consistency of reports spoke well for its trustworthiness

Of equal importance with the consideration of penile size and activity was the accurate observation of progression under treatment of qualitative changes

in the secondary sex characters, perhaps better designated as sex maturation. The participation of skeletal muscle, fat, mineral and water elements was clinically reflected in the alterations of height, weight and epiphyseal status. A most noteworthy manifestation, however, was the growth of hair on the various parts of the body.

The process of sex maturation is usually designated by the terms puberty, adolescence and maturity. Variations in the time required for sex maturation are well recognized. Some individuals develop from the status of children into fully mature men within a few years, while others may require 10 years or longer to negotiate the same transformation. The delay in

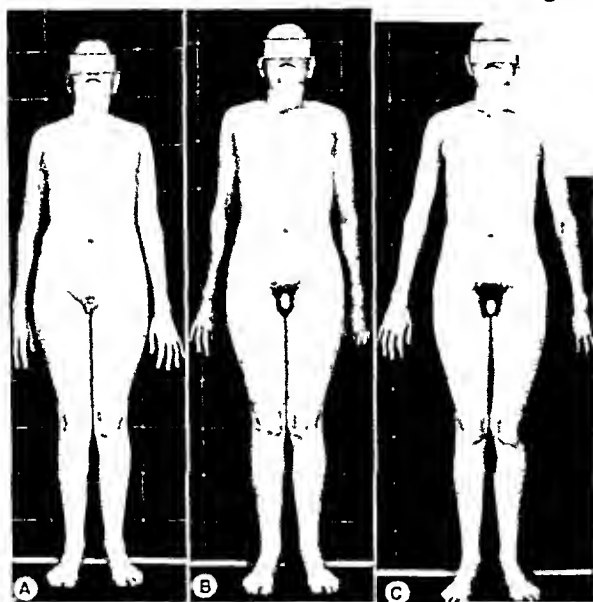


FIG. 1. STIMULATION OF GENITAL GROWTH AND MATURATION IN HYPOGONADISM. P.W., age 19. A. Prior to therapy. B. Five months after initiation of treatment with androgens. C. Eight months after initiation of treatment. Maximal genital growth attained prior to development of full thickness of the pubic hair.

the sequence of appearance of pubic, axillary, facial and chest hair may be increased. Extensions of the chest-hair growth frequently occur in men in their thirties and forties.

The period of pubic hair growth, from its first appearance to full thickening represents a most important and accelerated phase of the whole maturation process and, therefore, merits a special definition of puberty, namely, genital maturation.<sup>2</sup> More

<sup>2</sup> The terms genital maturation and pubic maturation are not identical. Genital maturation carries a broader connotation of a qualitative change of the genital tissues themselves. The term pubic maturation refers specifically to thickening of the pubic hair and is not identical with genital maturation, but is only a part of this process and offers an index to the progress of genital maturation.

sharply localized in its onset, duration and age span of occurrence than the subsequent body hirsutism, the time of its development offers a valuable point of orientation for evidences of other body changes. Occurring usually within the limits of 11 to 16 years of age (more frequently 12 to 14) and varying with hereditary, racial and climatic factors, the actual onset may be timed closely within an accuracy of 3 months, by the appearance of coarse public hairs subsequent to a fine, downy accentuation clinging to the surface of the pubis for the preceding 6 months to a year. The maximal mass of public hair is usually attained within 2 years or less; full thickening is here denoted by a roughly quantitative index of 4+ and the half-way point, correspondingly as 2+. As will be shown, estimation of actual pubic hair thickening in terms of that maximally expected for the type of individual, is of clinical value in the establishment of prognosis for genital growth.

## RESULTS

**Genital functions.** A rapid and most constant result of substitution therapy in male hypogonadism was the improvement of genital neurovascular and muscular functions. A rise in skin temperature, increased turgidity and irritability to spontaneous erection of the phallus became manifest within 48 hours. Maximal sensitivity to the hormone was noted in a) the younger age-groups, b) in individuals showing a greater degree of genital immaturity, and c) in one case of hypogonadism secondary to a pituitary and adrenocortical deficiency, in whom a single dose of 10 mg. of methyl testosterone at bedtime caused troublesome priapism overnight and next day. Generally, an average daily dose of 20 to 40 mg. of methyl testosterone was necessary for the maintenance of the desired neurovascular irritability, as well as the production of penile growth if this was to be attained at all.

Continuous and prolonged medication (over a period of 6 months) produced at times refractory periods during which spontaneous erectility disappeared while the libido and susceptibility to mechanical stimulations, as a masturbation, continued unimpaired. Rest for medication for one week appeared more effective in restoring spontaneous sensitivity than the stubborn continuation of the daily dose, or its increase to twice the previous level. Continuous dosage or over-dosage probably resulted in a waste of medication and at times also led to vague gastric distress.

In 4 cases the substitution of 12.5 mg. of testosterone propionate inunction (25 mg. of the active substance per gm. of base, applied at bedtime) for the oral type of therapy produced equally gratifying

results and was preferred by 2 patients because of a greater sense of well being and freedom from gastric discomfort.

Failure of spermatogenesis which is the rule in severe hypogonadism with rudimentary testes was, of course, not influenced by male hormone therapy.

**Genital size and pubic-hair maturation.** Definite penile growth as the result of substitution therapy was not attained in all cases. When it occurred, the first evidences appeared within a few weeks and the maximal limit was reached within 6 to 9 months. Progressive increases in the length and diameter of the organ were manifest both in the relaxed and erect state, with all measurements augmenting concomitantly. In cases in which the pubic hair growth was absent, or deficient (with the exception of cases 8, 9), thickening was produced to full density and its progress charted roughly in quantitative terms. Maximal results were attained within 6 months to 2 years.

The appearance of axillary, chest and facial hirsutism in succession was delayed, the occurrence of each phase depending on the fulfillment of the previous stage. Throughout the total period of observation stimulation of the growth of face and chest hair was the least satisfactory of all and inadequate at its best. Local application of testosterone propionate inunction to these areas did not prove effective.

Deepening of the voice was satisfactory and developed in the latter stages of pubic-hair thickening and afterwards.

An enlargement of the scrotum and corrugation of the scrotal skin irrespective of the testicular mass occurred early in the course of treatment, as did prostatic enlargement to a maximal point which was less than the average development for a normal male. During the first few weeks of treatment the soft and rudimentary testes became larger, congested, more firm and defined to palpation; later they regressed to their initial state.

Analysis of the clinical findings prior to treatment with emphasis on the distinction between genital size and pubic-hair maturation has made it possible to establish criteria of prognosis for the results of treatment. The extent or rapidity of the penile growth produced was not influenced by its initial size, nor by that of the testes, nor by excessive medication, the age of the individual or the number of years he had been genitally retarded. Nor was it apparently affected by any configuration factors of fat distribution or skeletal proportions.

Presence or absence of pubic hair and the rapidity of its thickening appeared to be the sole reliable determining factor for the prediction of penile growth. Penile growth could be elicited only when evidences

of public maturation<sup>2</sup> were not present or were incomplete. The penis had reached its maximal length at the half-way stage of pubic-hair thickening (2+). Penile growth was terminated or precluded at the time of full pubic hair density (4+).

The rapidity of the thickening of the pubic hair varied considerably and independently of the age of the individual, the testicular mass or the intensity of treatment above physiological accuracy; in some cases it required as long as 6 months for the early evidences (1+) and in others it progressed rapidly to completion (4+) within the same interval. In a

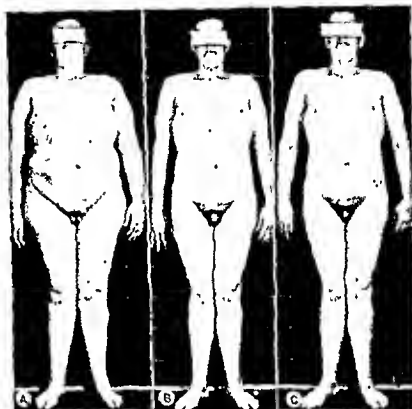


Fig. 2. STIMULATION OF GENITAL GROWTH AND MATURATION IN THE HYPOGONAD G.R., age 28. A. Prior to therapy. B. Eight months after initiation of treatment with androgens. C. Fifteen months after initiation of treatment. Maximal genital growth attained prior to development of full thickness of the pubic hair.

given case the speed of the process could not be accurately predicted, although it seemed somewhat more delayed in the slender and light-complexioned individual, which was probably dependent on so-called constitutional and hereditary factors.

**Effects on skin and body configuration.** The skin of the untreated hypogonadal individual was dry, poor in elasticity and luster. Substitution therapy, which promotes mineral and water storage, led to a marked improvement in tissue tone, with increased firmness to palpation, and surface sheen to inspection. There was a lightening of the grayish caste to the skin, particularly noted over areas poor in subcutaneous fat, as under the eyes. An increased surface moisture and oiliness became evident, with the latter particularly marked through the period of growth of pubic hair and at times becoming sufficiently severe to be associated with seborrhea and acne.

The adult hypogonadal male, in agreement with

accepted clinical impressions, was of average or better height. With or without treatment, closure of the epiphyses was delayed but eventually took place long after, and only if some evidences of pubic-hair maturation had occurred. Male hormone therapy in these cases produced an undeniable acceleration of growth, both in height and in breadth (shown in shoulder girdle and facial bones) only when the epiphyses were open and usually in conjunction with pubic maturation, namely, during or immediately after thickening of the pubic hair.

More often than not the hypogonad patient ap-

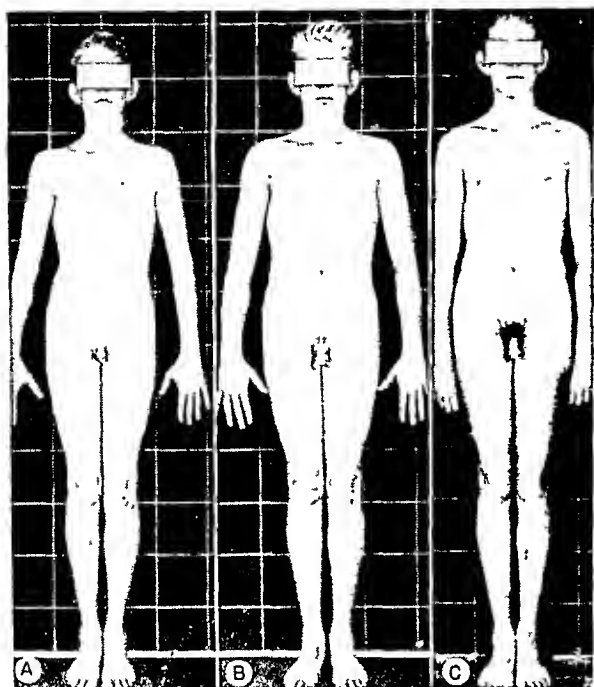


Fig. 3. STIMULATION OF GENITAL GROWTH AND MATURATION IN THE HYPOGONAD J.H., age 18. A. Prior to therapy. B. Six months after initiation of treatment with androgens. C. Eighteen months after initiation of treatment. Maximal genital growth attained prior to development of full thickness of pubic hair.

peared to be stout or obese with accumulations of fat over the chest, abdomen and hips, to an increasing degree with age. Although a feminine type of fat distribution, including mammary prominence (adipose or glandular), was not infrequent and may even be pronounced in normal individuals, it appeared to be more prevalent in the older obese type of hypogonad male. Improvement in body configuration resulted through weight loss on low-calorie diets. Improvement could also be induced, in spite of weight gain, with male hormone stimulation if further muscle development and skeletal growth could occur, usually in conjunction with thickening of the pubic hair. Marked improvements in configuration appeared in the initially lean hypogonad person, in whom pubic maturation was produced with the

male hormone when the additive anabolic effects of hydration, fat, muscle and bone storage resulted in striking body changes and weight gain. Initially, as well as following treatment, the somatic pattern at its best remained at all times within the framework of hereditary trends which appeared to be of a paramount significance.

**Personality.** The personality of the adult hypogonad was masculine in a sense that his interests and activities were masculine. There were no evidences of homosexual trends or the feminine type of behavior. Curiosities were directed toward the opposite sex but the contacts were avoided because of the feebleness of sex impulse and feeling of inadequacy. Impulse life, in general, as expressed in 'drive' was weak or poorly sustained, due to true fatigability in some cases, possibly to a specific effect of male hormone deficiency. Moreover, a knowledge of genital insufficiency projected itself into a sense of inadequacy toward the environment as a whole, undermining ego evaluation and creating a feeling of self-reference of inferiority. At times, periods of acute anxiety or depression occurred, but major psychoses have not been found. Compensatory behavior may become manifest at any stage of this process and, as in all bodily disabilities, depending on the type, character, intelligence and temperament of the individual, it may be an asset or detriment to his personality. It is a mistake, however, to blanket the behavior of the hypogonad under the expression 'compensating for inferiority.' Since intelligence, temperament and character in these individuals were not inherently abnormal, but followed constitutional and hereditary lines, the hypogonad sooner or later gained insight into the specific nature of his disability, and made a fairly satisfactory occupational and social adjustment to his environment.

Substitution therapy with male hormone increased the sex-urge both in its psychic and physical aspects and led to some masturbatory activity and eventually to a cautious contact with the opposite sex. The prime concern of the patient in all cases was the development of adequate penile growth in order to pass as normal in appearance and performance. An increase in energy and sense of well being promoted optimism, stronger drive and aggressiveness in dealing with the environment. At times this response almost suggests a specific effect of the male hormone comparable to the specificity of benzedrine sulphate to produce a similar reaction. It must be taken into consideration, however, that a discovery of an antidote to the feeling of inadequacy is of sufficient psychogenic strength to produce the same result. Certain it is that the hypogonad under treatment was a much happier individual.

## DISCUSSION

Unless a history of infection, damage or castration is available, the cause of testicular deficiency often is not well understood and may be ascribed to hormonal and developmental factors. Thus, a fat boy with hypogonadism before puberty has been termed a 'hypopituitary' and promoted into a eunuch or 'eunuchoid' if the genitalia remain small as his legs grow long after puberty. Should he surmount both classifications in spite of subsequent accumulation of fat over chest and hips, he will then be advanced into a 'constitutional type,' in which he may have belonged in the beginning, provided the genital status is given a charitable interpretation by the physician. The triad of 'pituitary-eunuchoid-constitutional' has been overworked to explain the response of one patient to the pituitary-like sex hormone, that of another to the male hormone and of a third to neither substance. In many gonadal problems the determination of where constitutionality begins, functional abnormalities continue and pathological changes take over is often difficult, if not impossible, because of the over-lapping of all processes. Undeniable familial repetitions of patterns of structure and function of the body *status quo* and change is covered by the concept of constitution. Obviously, it is operable in normality, precipitation of disease and response to treatment; in any endocrine problem it includes both the variations in the peripheral tissues as well as the glands themselves.

This undoubtedly contributes to the clinical variable in hypogonadism and response to treatment. Observations during the past 5 years have demonstrated that the male may present problems of the reproductive system as highly specialized as those of the female. Endocrine aspermia, gynecomastia and penile hypoplasia have been noted as a solitary disturbance both in the normal male and in the adrenogonadal type. In genital problems as a whole the distinction between genital (penile) growth, function and thickening of the pubic hair can be profitably stressed, not only to demonstrate their orderly relationships but their disassociations.

The adaptability of pubic hair thickening to a roughly quantitative evaluation in its onset and progression qualifies it for use in a specific definition of genital maturation at puberty, and as a reference point in the orientation of somatic and endocrine disturbance of early adulthood.

The hormonal causes of thickening of pubic hair are open to speculation. Association of this process with marked acceleration of growth of other tissues (penile, testicular, skeletal, muscular) suggests a multiplicity of physiologic causes ranging from the pituitary, if not the hypothalamus, down the scale. While

the male hormone plays a dominant rôle in genital (penile) growth and neurovascular irritability, it probably acts in a contributory manner only in genital maturation.<sup>2</sup> Administration of male hormone to younger children causes increased penile growth and irritability but does not produce pubic hair growth; and, conversely, a considerable degree of thickening of pubic hair may be found in some young adults in spite of marked evidence of a male hormone deficiency. The termination of potential penile growth synchronous with the development of the full thick-

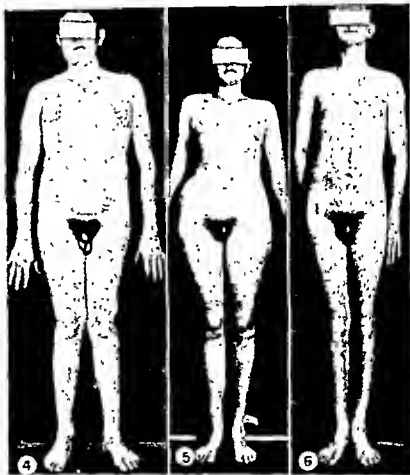


Fig. 4-6. FAILURE TO PRODUCE GENITAL GROWTH IN HYPOGONAD MALES in the presence of adequate to full thickness of the pubic hair. Period of treatment, 4 months. 4. E.S., age 18. 5. R.M., age 20. 6. J.B., age 19.

ness of the pubic hair as observed here, actually suggests a possible antagonism in the causative factors.

Further evidence for the distinctiveness of the penile growth factor (male hormone) and that which causes genital maturation is presented by cases with marked delay in maturation progression in the presence of normal to excessive genital growth. This is demonstrated by the cases of tall boys 18 to 20 years of age who have excellent genital size but scanty pubic hair growth, and no chest and face hair (6 cases, unpublished).

In 2 cases of hypogonadism secondary to pituitary deficiency (in one case associated with a secondary Addison's disease) which have been treated with male hormone substitution therapy, favorable response in genital growth and irritability have been obtained, but not thickening of the pubic hair has occurred. The fact that there is a relationship of the

adrenal cortex to pathological hirsutism is well established. These evidences point to some cause other than the male hormone in the production of genital maturation (puberty), possibly to some 'maturity factor' in the adrenal cortex.

The distinction between genital size and genital maturation is of importance, not only in the prediction of genital growth through the action of the male hormone, but also in the exercise of greater caution in attributing other accelerated growth phenomena (skeletal) to this substance alone, when evidences of genital maturation in terms of pubic hair thickening are also progressing.

#### SUMMARY

1. The distinction between genital growth (penile growth) and genital maturation as revealed by pubic hair thickening is emphasized.

2. Genital growth is directly under the influence of the androgenic hormone of the testes or its exogenous substitutes. It may be produced in the absence of, as well as in the presence of partial genital maturation as gauged by thickening of the pubic hair, but it is definitely precluded by the evidences of full genital maturation in terms of pubic hair thickening. Observation of the degree of pubic hair maturation, therefore, offers a valuable clinical criterion for the prognosis of genital growth, both in the hypogonad under treatment and in the normal individual as well.

3. Genital maturation is only partly under the influence of the androgenic hormone of the testes or its exogenous substitutes. It is precipitated by this hormone only when delayed, and in the presence of an adequacy of other necessary 'maturity factors,' the nature of which is open to speculation. It is assumed that the full development of these maturity factors is responsible for the eventual termination of genital growth.

4. Methyl testosterone is a potent substitute for the androgenic hormone of the testes and stimulates genital growth and maturation when an endogenous deficiency of this substance is present and within the limits of the above-mentioned considerations. Its effectiveness in increasing the genital neurovascular irritability is more constant and depends upon the presence of an initial male hormone deficiency only.

Dosage, technique of medication and side effect are discussed.

5. Testosterone propionate inunction (25 mg. per gm. of base) appears to be equally effective in maintenance of the hypogonad, requiring less of the active substance than the use of methyl testosterone orally; it is preferable in some cases because of the absence of side effects.

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# Effect of Chorionic Gonadotropic Hormone and of Male Sex Hormone on Height Increase and Bone Development

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ATTENTION HAS BEEN focused in recent years on the effects of gonadotropic and sex hormones on somatic growth, especially on height and bone development. While the exact mode of action is unknown, the following may be possible factors a), the inherent growth-stimulating qualities which affect other somatic tissues as well as the accessory sex organs, b), stimulation of the growth producing factors of the anterior pituitary gland or inhibition of the gonadotropic function of this gland with subsequent suppression of the growth function. According to Severinghaus (1) the injection of pregnancy urine preparations and of gonadal hormones have an effect on both the acidophilic and basophilic cells of the anterior lobe of the pituitary gland, although males and females do not respond similarly in all cases. The acidophilic cells, which are concerned with growth function, may also be a source of one of the two gonad-stimulating hormones of the anterior pituitary gland.

Castration of male rats in early life leads to significant inhibition of general somatic development with a resultant decrease in weight and retardation in body length as compared to normal controls. Rubinstein and co workers (2) report that testosterone propionate in small daily intraperitoneal injections has a stimulating effect on the growth of these castrated rats but that large doses produce a depressing effect which exceeds that of castration alone. Dosage and duration of treatment are important factors as this depression is not observed until the 24th day at which time it becomes progressively more marked.

Turner and associates (3) found that large doses of testosterone propionate given over prolonged periods of time, even when treatment was started one day after birth, did not accelerate body growth or skeletal

maturation in rats, except in isolated bones. At the end of the period of observation the rate of osseous development was not increased to any greater extent than in control animals.

Clinical manifestations of the growth stimulating effect of gonadotropin and of sex hormones are noted in both sexes at puberty in the physiological spurt of linear and general somatic growth, in addition to an increase in the size of the external and internal sex organs. Precocious puberty and increased activity of the gonads are associated with marked acceleration in both height and bone development for a short period and subsequent dwarfing occurs due to premature closure of the epiphyses. Prepubertal eunuchoidism, on the other hand, is characterized by delay in closure of the epiphyses. The resultant height depends on the functional activity of the anterior-pituitary growth hormone. Eunuchoid gigantism ensues in the presence of an associated increased pituitary activity, while dwarfism occurs if the amount of growth hormone is insufficient.

Increase in height has been reported in sexually underdeveloped and underweight boys following the administration of testosterone propionate by injection (4-7), of methyl testosterone by mouth (8) and of chorionic gonadotropic hormone by injection (5, 7, 9, 10, 11).

Variable results have been reported on the effect of chorionic gonadotropin and of testosterone propionate on the excessive height of boys with eunuchoidism or other forms of milder hypogonadism. Both successful and unsuccessful curbing of height increase have been observed (5, 7).

The action of chorionic gonadotropic hormone and of testosterone propionate on osseous development and on epiphyseal closure has also been studied in association with the effects on height. McCullagh (12) originally felt that testosterone propionate did



not affect epiphyseal development, but he now considers that, although small doses (15 to 60 mg. per week) fail to accelerate epiphyseal changes, large doses (105 mg. per week) cause a marked increase in epiphyseal age. Although the latter statement is made on the basis of observations in adult eunuchoid men in whom the epiphyses were still ununited, he warns against the use of large doses of testosterone propionate in individuals who have not as yet obtained normal adult stature, for fear of stunting of growth.

considered as instances of pseudo-cryptorchidism and are not included.

In evaluating the results in cases of cryptorchidism, a testis was considered to be completely descended when it entered into the scrotum and remained there. Descent as far as the external ring or to the upper border of the scrotum was listed as partial descent. In a few instances, the testis descended into the scrotum and then retracted, but eventually remained in the scrotum after further treatment. In these cases,

TABLE 1. SUMMARY OF RESULTS IMMEDIATELY AFTER THERAPY

| Case No.   | Initial Age yr., mo. | Initial Height <sup>1</sup> | Initial Bone Age <sup>1</sup> | Percent-age In-crement in Height | Percent-age In-crement in Bone Age | Height at End of Treat-ment <sup>1</sup> | Bone Age at End of Treat-ment <sup>1</sup> | Treatment      |                        | Diagnosis                                 |   |
|--|----------------------|-----------------------------|-------------------------------|----------------------------------|------------------------------------|--|--|----------------|------------------------|---|---|
|  |                      |                             |                               |                                  |                                    |  |  | Dura-tion, mo. | Total Dosage R.U.; mg. |   |   |
| Group 1, receiving chorionic gonadotropin; R.U.  |                      |                             |                               |                                  |                                    |  |  |                |                        |   |   |
| 4  | 9-0                  | +                           | N                             | -35                              | +25                                | +  | N  | 7              | 11,600                 | Cryptorchidism                            |   |
| 5  | 9-6                  | +                           | N                             | +18                              | +50                                | +  | +  | 11             | 35,600                 | Cryptorchidism                            |   |
| 6  | 10-9                 | +                           | N                             | +50                              | +160                               | +  | +  | 13             | 36,800                 | Cryptorchidism                            |   |
| 7  | 14-3                 | +                           | N                             | +69                              | +30                                | +  | N  | 5              | 20,000                 | Cryptorchidism                            |   |
| 9  | 12-0                 | -                           | N                             | 0                                | 0                                  | -  | N  | 13             | 40,400                 | Cryptorchidism, adiposo-genital dystrophy |   |
| 14   | 11-0                 | +                           | N                             | +29                              | +12                                | +  | N  | 22             | 60,000                 | Adiposogenital dystrophy                  |   |
| 16   | 9-10                 | N                           | -                             | +11                              | +20                                | N  | -  | 16             | 17,000                 | Adiposogenital dystrophy                  |   |
| 17   | 10-0                 | +                           | N                             | -25                              | 0                                  | N  | N  | 6              | 11,800                 | Adiposogenital dystrophy                  |   |
| 18   | 11-0                 | +                           | N                             | 0                                | 0                                  | +  | N  | 13             | 26,000                 | Adiposogenital dystrophy                  |   |
| 22   | 9-0                  | -                           | -                             | +12½                             | +100                               | -  | N  | 5              | 20,000                 | Adiposogenital dystrophy                  |   |
| Group 2, receiving both chorionic gonadotropin, R.U., and testosterone propionate, mg. |                      |                             |                               |                                  |                                    |  |  |                |                        |   |   |
| 1  | 10-11                | +                           | +                             | +38                              | +18                                | +  | +  | 24             | 12,200                 | 1,470                                     | Eunuchoidism                                |
| 3  | 8-4                  | +                           | -                             | +40                              | +81                                | +  | -  | 18             | 19,000                 | 250                                       | Cryptorchidism                              |
| 10   | 9-6                  | +                           | N                             | +5                               | 0                                  | +  | N  | 32             | 95,000                 | 225                                       | Adiposogenital dystrophy                    |
| 11   | 10-2                 | +                           | +                             | +50                              | +50                                | +  | +  | 11             | 18,000                 | 290                                       | Adiposogenital dystrophy                    |
| 12   | 15-6                 | -                           | -                             | +156                             | 0                                  | -  | -  | 18             | 27,000                 | 250                                       | Adiposogenital dystrophy with short stature |
| 13   | 14-0                 | +                           | N                             | +40                              | 0                                  | +  | N  | 15             | 10,250                 | 590                                       | Adiposogenital dystrophy                    |
| 15   | 10-10                | +                           | -                             | -27                              | +33                                | +  | N  | 15             | 13,000                 | 350                                       | Adiposogenital dystrophy                    |
| 19   | 12-0                 | +                           | N                             | +100                             | +133                               | +  | +  | 14             | 5,000                  | 820                                       | Adiposogenital dystrophy                    |
| 21   | 8-0                  | +                           | -                             | +44                              | +116                               | +  | +  | 36             | 17,500                 | 250                                       | Adiposogenital dystrophy                    |
| 24   | 11-6                 | +                           | -                             | +33                              | +50                                | +  | N  | 24             | 49,000                 | 260                                       | Adiposogenital dystrophy                    |

<sup>1</sup> Plus and minus signs indicate a height and bone age above or below the normal for that age; N, normal for the age.

Others state that moderate amounts of male sex hormones or of chorionic gonadotropic hormone do not produce progressive epiphyseal development or premature epiphyseal closure (6, 14-19).

The present report is concerned with the effects of chorionic gonadotropic hormone, with or without testosterone propionate, on the height and bone development of 20 boys who were treated for cryptorchidism and hypogenitalism.

The results on the descent of the testes and the growth of the external genitalia are discussed in a separate communication (20). All cases of cryptorchidism in this series are of the true type. Testes of the receding type, or those which could be forced into the scrotum by either manipulation or heat are

the latter date was considered as that of complete descent.

The conditions present in these boys consisted of adiposogenital dystrophy, 11 instances; eunuchoid type of adiposogenital dystrophy, 2; primary hypogonadism with giantism, 1; and cryptorchidism, 15 cases. The ages ranged from 8 to 15½ years. Fifteen were below the age of 12 years and 5 were above this age.

Roentgenograms were made of the skull and sella turcica and of the wrists at the initiation of treatment, and of the wrists at varying intervals. The bone development was measured by a modification of Todd's Standards (21), and the height by the Baldwin-Wood Standards for the medium average (22).

Treatment was given for periods ranging from 5 to 36 months and was continuous for the first 3 months and interrupted thereafter, especially during the summer months. One group of 10 boys received intramuscular injections of chorionic gonadotropic hormone<sup>1</sup> in doses of 250 to 500 rat or international units twice a week, with an average of 28,380 units. The second group of 10 boys had been treated with chorionic gonadotropic hormone but had not responded favorably with either the descent of the

The total dosage of chorionic gonadotropic hormone in this group ranged from 5000 to 95,000 rat or international units, with an average of 26,595, that of testosterone propionate ranged from 225 to 1470 mg, with an average of 475.5 mg. The average dosage of chorionic gonadotropic hormone for both groups was 27,487 units.

## RESULTS

*Height.* There was an increase in height in every

TABLE 2. EFFECT OF TREATMENT ON HEIGHT

| Case No  | Chronological Age Initially yr, mo | End of treatment yr, mo | Height, inches Initially | End of treatment | Normal Height for Same Ages, in | Increment, in, Above and Below Normal | Percentage Increment Above and Below Normal |
|--|------------------------------------|-------------------------|--------------------------|------------------|---------------------------------|---------------------------------------|---|
| <i>Group 1, Chorionic gonadotropin</i>                             |                                    |                         |                          |                  |                                 |                                       |   |
| 4  | 9-0                                | 11-0                    | 56                       | 58½              | 52                              | -1 4                                  | -35   |
| 5  | 9-6                                | 11-6                    | 56½                      | 61½              | 53                              | +0 75                                 | +18   |
| 6  | 10-9                               | 12-6                    | 62½                      | 67½              | 55½                             | +1 62                                 | +50   |
| 7  | 14-3                               | 15-0                    | 65½                      | 68½              | 61½                             | +1 38                                 | +69   |
| 9  | 12-0                               | 13-3                    | 52                       | 54½              | 58                              | N                                     | 0   |
| 14   | 11-0                               | 13-8                    | 60                       | 67½              | 56                              | +1 75                                 | +29   |
| 16   | 9-10                               | 12-3                    | 53½                      | 58½              | 53½                             | +0 5                                  | +11   |
| 17   | 10-0                               | 11-6                    | 54½                      | 57               | 54                              | -0 75                                 | -25   |
| 18   | 11-0                               | 12-0                    | 58                       | 60               | 56                              | N                                     | 0   |
| 22   | 9-0                                | 11-0                    | 49                       | 53½              | 52                              | +0 50                                 | +12½  |
| <i>Group 2, Chorionic gonadotropin and testosterone propionate</i> |                                    |                         |                          |                  |                                 |                                       |   |
| 1  | 10-11                              | 13-4                    | 67                       | 74½              | 56                              | +3 0                                  | +38   |
| 3  | 8-4                                | 9-6                     | 51                       | 55½              | 50                              | +1 25                                 | +40   |
| 10   | 9-6                                | 14-0                    | 54                       | 64½              | 53                              | +0 5                                  | +5  |
| 11   | 10-2                               | 11-2                    | 58                       | 61               | 54½                             | +1 0                                  | +50   |
| 12   | 15-6                               | 17-0                    | 60½                      | 65½              | 66                              | +3 12                                 | +156  |
| 13   | 14-0                               | 15-3                    | 65                       | 68½              | 63                              | +1 0                                  | +40   |
| 15   | 10-10                              | 14-0                    | 59½                      | 65½              | 55½                             | -1 75                                 | -27   |
| 19   | 12-0                               | 13-2                    | 60½                      | 65               | 58                              | +2 25                                 | +100  |
| 21   | 8-0                                | 11-0                    | 53                       | 61½              | 50                              | +2 12                                 | +44   |
| 24   | 11-6                               | 13-6                    | 58½                      | 64½              | 57                              | +1 5                                  | +33   |

testes or the growth of the external genitalia. They received testosterone propionate<sup>2</sup> in doses of 10 to 25 mg twice a week. This therapy was continued for 4 to 8 weeks and was then discontinued to be replaced by chorionic gonadotropic hormone for 1 to 3 months. This alternation was adhered to throughout the entire course of treatment except for intervals lasting from several weeks to several months, especially during the summer. In a few instances, only testosterone propionate was administered after the initial 3 month period of treatment with gonadotropic hormone.

<sup>1</sup> The chorionic gonadotropin was supplied by a) Roche-Organon Inc., Nutley, N. J. (Pregnyl), b) E. R. Squibb & Sons, New Brunswick, N. J. (Follutein) and c) Ayerst, McKenna & Harrison, Rousses Point, N. Y. (A.P.L.)

<sup>2</sup> The testosterone propionate was supplied by a) Roche-Organon Inc., Nutley, N. J. (Neo Hombreol) and b) The Schering Corp., Bloomfield, N. J. (Oretol).

boy. This increase was above the normal expectancy in 14 cases, normal in 3 and below normal in 3. The average gain in height for the entire series was 32.2 per cent above the normal increment. In the 10 boys treated with chorionic gonadotropic hormone the average increase in height was 12.9 per cent above the normal increment, 6 of these showed a gain ranging from 1.1 to 69 per cent above the normal, 2 grew at a normal rate and 2 increased in height at a rate lower than the normal.

Better results were obtained with the boys who received the combined treatment of chorionic gonadotropic hormone and testosterone propionate, as shown by an average of 47.9 per cent increase above the normal increment, 8 of these boys showed a gain in height ranging from 3.3 to 156 per cent above the normal rate, one showed a slight increase above the normal and one a lower rate than normal.

TABLE 3. EFFECT OF TREATMENT ON OSSEOUS DEVELOPMENT

| Case No.  | Chronological Age  |                           | Bone Age, yr., mo. |                  | Actual Change, yr.            | Gain Above Normal, yr. | Percentage Gain Above Normal |
|---|--------------------|---------------------------|--------------------|------------------|-------------------------------|------------------------|------------------------------|
|   | Initially yr., mo. | End of treatment yr., mo. | Initially          | End of treatment |                               |                        |                              |
| Group 1, Chorionic gonadotropin                             |                    |                           |                    |                  |                               |                        |                              |
| 4   | 9-0                | 11-0                      | 8-6                | 11-0             | 2.5                           | +0.5                   | +25                          |
| 5   | 9-6                | 11-6                      | 10-0               | 13-0             | 3.0                           | +1.0                   | +50                          |
| 6   | 10-9               | 12-6                      | 10-6               | 15-0             | 4.5                           | +2.8                   | +160                         |
| 7   | 14-3               | 15-0                      | 14-3               | 15-3             | 1.0                           | +0.25                  | +30                          |
| 9   | 12-0               | 13-3                      | 12-0               | 13-0             | 1.0                           | N                      | 0                            |
| 14  | 11-0               | 13-8                      | 11-0               | 14-0             | 3.0                           | +0.3                   | +12                          |
| 16  | 9-10               | 12-3                      | 8-0                | 11-0             | 3.0                           | +0.5                   | +20                          |
| 17  | 10-0               | 11-6                      | 10-0               | 11-6             | 1.5                           | N                      | 0                            |
| 18  | 11-0               | 12-0                      | 11-0               | 12-0             | 1.0                           | N                      | 0                            |
| 22  | 9-0                | 11-0                      | 7-0                | 11-0             | 4.0                           | +2.0                   | +100                         |
| Group 2, chorionic gonadotropin and testosterone propionate |                    |                           |                    |                  |                               |                        |                              |
| 1   | 10-11              | 13-4                      | 12-3               | 15-0             | 2 <sup>3</sup> / <sub>4</sub> | +0.4                   | +18                          |
| 3   | 8-4                | 9-6                       | 6-6                | 8-6              | 2                             | +0.9                   | +81                          |
| 10  | 9-6                | 14-0                      | 9-6                | 14-0             | 4 <sup>1</sup> / <sub>2</sub> | N                      | 0                            |
| 11  | 10-2               | 11-2                      | 11-3               | 12-9             | 1 <sup>1</sup> / <sub>2</sub> | +0.5                   | +50                          |
| 12  | 15-6               | 17-0                      | 14-0               | 15-6             | 1 <sup>1</sup> / <sub>2</sub> | N                      | 0                            |
| 13  | 14-0               | 15-3                      | 14-0               | 15-3             | 1 <sup>1</sup> / <sub>4</sub> | N                      | 0                            |
| 15  | 10-10              | 14-0                      | 9-10               | 14-0             | 4 <sup>1</sup> / <sub>6</sub> | +1.0                   | +33                          |
| 19  | 12-0               | 13-2                      | 12-0               | 15-6             | 3 <sup>2</sup> / <sub>2</sub> | +2.0                   | +133                         |
| 21  | 8-0                | 11-0                      | 6-6                | 13-0             | 6 <sup>1</sup> / <sub>2</sub> | +3.5                   | +116                         |
| 24  | 11-6               | 13-6                      | 10-0               | 13-0             | 3                             | +1.0                   | +50                          |

This greater stimulus to growth in height in the second group is evidently due to the action of testosterone propionate. Analysis of the data for this group reveals that those who received larger doses of testosterone propionate, more than 500 mg. throughout the the course of treatment, showed a gain of 59.3 per cent above the normal increase in height, while those who received less than this amount attained an average height of 43 per cent above that of normal expectancy.

*Relation of original height to results.* Before treatment was started, 16 boys were above the height normal for their age. The case of one boy with primary hypogonadism, who was 11 inches above the average height for his age, will be discussed in detail later; one other boy was 6.5 inches above the normal height for his age and grew at a rate of 50 per cent above the normal increment; 4 boys were between 3¾ and 4¼ inches above the average height and grew at rates varying from 35 per cent below the normal increment to 29 per cent above normal expectancy. The remainder of the boys in this group were between 1 and 3 inches above the normal average medium height. The average increase in height for this group of originally overheight boys was 29.8 per cent above the normal increment. At the termination of treatment, 15 were above the average medium height for their ages and one was normal in height.

One boy whose height was normal at the start of treatment showed an increase of 11 per cent above the normal expectancy at the termination of therapy. Three boys were 6, 3, and 5 inches, respectively, below the average height before treatment and grew at a rate of normal, slightly above the normal and 156 per cent above the normal increment, respectively, but all 3 were still below the average medium height for their age at the termination of treatment. The average increase in height for this group was 56.2 per cent above the normal increment.

*Bone development.* The bone development before treatment was started was normal in 11 boys, advanced in 2 and retarded in 7. During the period of treatment it progressed at a normal rate in 6 boys, at an accelerated speed above the normal in 14 and in no case was it below the normal. The average increase was 43.9 per cent above the normal increment and was greater in those receiving both hormones (48.1%) than in those obtaining only chorionic gonadotropin (39.7%). In the former group, the range was from 12 to 160 per cent above the normal expectancy and in the latter, from 18 to 133 per cent. The greater stimulus to bone growth, with reference to height increase, evidently is also due to the action of testosterone propionate.

At the termination of the period of treatment, 6 boys showed an advanced bone development, 11 a normal bone age and 3 a retarded bone age. In the

original normal group 3 showed an advanced bone age and 8 a normal bone development, the average increase for this group was 39 per cent above the normal increment. Both of the boys with an initially advanced bone age showed still further acceleration at the termination of treatment but the average increase was no greater than that in the normal group (38 per cent above the normal increment). The increase in height in the originally retarded group ranged from normal to 100 per cent with an average of 53 per cent above the normal, but only 1 case showed an advanced bone age at the termination of treatment, 3 were normal and 3 were still retarded.

*Relation of linear to osseous growth* On the basis of percentage increase above the normal, the response in the rate of bone development was greater than that of height, on the average, but not in individual instances. The increase was greater in osseous development than in height in 11 instances, less in 6 and approximately the same in 3.

There is no constant relationship between the

effect of treatment on height as compared to that on bone development. Both boys whose bone development was advanced before treatment showed an advance both in bone age and height above the normal at the end of the period of treatment. Those who were normal in bone development showed an ultimate advance in height in 9 instances, and in bone age in 3 instances. In the group with retarded bone development, 4 attained overheight and only one an accelerated bone development. This lack of correlation is also evident when the cases are considered from the viewpoint of height. Of the 16 boys who were overheight before treatment, 15 were overheight at the end, but only 6 showed an ultimate advance above the normal in bone age. On the basis of percentage increase, apparently the greatest advance in bone age occurred in those who were overheight and the greatest increase in height took place in those who were originally advanced in bone age. The next greatest increase is noted in those who were retarded either in bone development or height at the beginning

TABLE 4. FOLLOW UP OBSERVATION AFTER TREATMENT WAS DISCONTINUED

| Height  |                           |            |                                  |                                    | Osseous Development |                   |                                     |                                       |
|---|---------------------------|------------|----------------------------------|------------------------------------|---------------------|-------------------|-------------------------------------|---------------------------------------|
| Case No   | Chronological Age, yr, mo | Height, in | Increment Above and Below Normal | % Increment Above and Below Normal | Bone Age, yr, mo    | Actual Change, yr | Gain or Loss Above and Below Normal | % Gain or Loss Above and Below Normal |
| Group 1, chorionic gonadotropin                             |                           |            |                                  |                                    |                     |                   |                                     |                                       |
| 4   | 14-0                      | 65½        | -0 5                             | -3%                                | 14-0                | 3                 | N                                   | 0                                     |
| 5   | 12 11<br>14-2             | 64½<br>67½ | N<br>N                           | 0<br>0                             | 14-0                | 1                 | N                                   | 0                                     |
| 6   | 11 6<br>14-9              | 70½<br>72½ | +1 1<br>-1 5                     | +44<br>-45                         | 16-0<br>17-0        | 1<br>1            | N<br>N                              | 0<br>0                                |
| 7   | 15 6<br>16-10             | 69<br>70   | -0 25<br>-0 8                    | -50<br>-44                         | 16-0<br>17-0        | 75<br>1           | +0 25<br>-0 3                       | +50<br>-21                            |
| 16  | 14-4                      | 63½        | N                                | 0                                  | 13-6                | 2 5               | +0 5                                | +25                                   |
| 17  | 12-6                      | 59½        | +0 75                            | +37 5                              | 13 0                | 1 5               | +0 5                                | +50                                   |
| 18  | 13-1<br>13-8              | 63½<br>65½ | +1 0<br>+0 37                    | +50<br>+18                         | 13-6<br>14-0        | 1 5<br>5          | +0 4<br>N                           | +36<br>0                              |
| Group 2, chorionic gonadotropin and testosterone propionate |                           |            |                                  |                                    |                     |                   |                                     |                                       |
| 1   | 14-10<br>15-6             | 78<br>78½  | -1 9<br>-0 2                     | -34<br>-28                         | 16-6<br>17-0        | 1 5<br>5          | +0 4<br>N                           | +36<br>0                              |
| 3   | 10 6                      | 57½        | -0 3                             | -10                                | 9-6                 | 1                 | N                                   | 0                                     |
| 10  | 14-10<br>17-0             | 65½<br>68½ | -0 7<br>-0 3                     | -38<br>-9                          | 15-0<br>17-0        | 1<br>2            | +0 2<br>N                           | +25<br>0                              |
| 11  | 13-2                      | 62½        | -1 37                            | -45                                | 14 0                | 1 25              | -0 75                               | -38                                   |
| 15  | 14-6                      | 66½        | +0 3                             | +30                                | 15-3                | 1 25              | +0 75                               | +150                                  |

TABLE 5. RELATIONSHIP OF INITIAL BONE DEVELOPMENT AND HEIGHT

| At Beginning of Treatment |           | At Termination of Treatment |        |          |  |                 |        |          |  |
|---------------------------|-----------|-----------------------------|--------|----------|--|-----------------|--------|----------|--|
|                           |           | Bone Development            |        |          | Average percentage increase above normal | Height          |        |          | Average percentage increase above normal |
|                           |           | Advanced                    | Normal | Retarded |  | Advanced        | Normal | Retarded |  |
| Bone development          | No. cases | Number of Cases             |        |          |  | Number of Cases |        |          |  |
| Advanced                  | 2         | 2                           | 0      | 0        | 38                                       | 2               | 0      | 0        | 44.0                                     |
| Normal                    | 11        | 3                           | 8      | 0        | 39                                       | 9               | 1      | 1        | 22.8                                     |
| Retarded                  | 7         | 1                           | 3      | 3        | 53                                       | 4               | 1      | 2        | 38.5                                     |
| Height                    |           |                             |        |          |  |                 |        |          |  |
| Advanced                  | 16        | 6                           | 9      | 1        | 47.4                                     | 15              | 1      | 0        | 29.8                                     |
| Normal                    | 1         | 0                           | 0      | 1        | 20.0                                     | 0               | 1      | 0        | 11.0                                     |
| Retarded                  | 3         | 0                           | 2      | 1        | 33.0                                     | 0               | 0      | 3        | 56.0                                     |

of treatment. This would indicate that a greater stimulation is exerted on those already advanced and those retarded than on the normal in either bone development or height.

*Age at beginning of treatment.* The age at which treatment was instituted had an effect on both the height and bone development. Better results were obtained in height increase in boys above 12 years of age than in those below this age, in spite of the shorter duration of treatment and greater amount of chorionic gonadotropic hormone administered. The dosage of male sex hormone was slightly larger. The results can be explained on the basis of the added stimulation of the puberty spurt and they confirm the observations of others (11).

The percentage of increase in bone development was above the normal in both age groups, but it was less in boys above 12 years of age than in those below this age. The administration of both hormones had a greater effect on height and on bone development, irrespective of age, than that of chorionic gonadotropin alone.

*Duration of treatment.* The average duration of treatment was 16.2 months for the series; 11.8 months for the group which received chorionic gonadotropic hormone and 20.7 months for the boys who obtained testosterone propionate in addition.

In analyzing the results with reference to the duration of treatment, it was decided to exclude the cases of the 3 boys who received large doses of testosterone propionate, as these amounts are not usually given to boys of this age. The average figures for the remaining 17 patients show a height increase above the normal increment of 17 per cent in those treated less than 12 months and of 31 per cent for those treated more than 12 months. There is an increasing percentage above the normal increment from 6 months to 2 years of treatment but not beyond this period. The results obtained in short periods of treatment are not con-

stant, for in the 3 patients who were treated for 5 to 7 months, the increase in height was a) normal, b) 35 per cent below the normal increment and c) 69 per cent above that of normal expectancy, respectively.

The rate of bone development likewise was affected by the duration of treatment, as evidenced by an average of 38 per cent increase above the normal increment in cases treated less than 12 months and of 46 per cent increase above the normal increment in those treated more than 12 months.

*Dosage.* The effects of the dosage of chorionic

TABLE 6. RELATIONSHIP BETWEEN EFFECT OF TREATMENT ON CRYPTORCHIDISM AND HYPOGENITALISM AND ON INCREASE IN HEIGHT AND BONE DEVELOPMENT

| No. of Cases   | Results                   | Average Percentage Height Increase Above Normal Increment | Average Percentage Increase in Bone Development Above Normal Increment |
|----------------|---------------------------|---|--|
| Cryptorchidism |                           |   |  |
| 6              | Complete descent          | 19.5  | 51.0   |
| 6              | Partial descent           | 26.6  | 49.5   |
| 3              | No effect                 | 14.0  | 62.0   |
| Hypogenitalism |                           |   |  |
| 9              | Marked effect             | 34.0  | 47.0   |
| 11             | Moderate or slight effect | 28.0  | 42.0   |

gonadotropic hormone were analyzed in 17 patients who received this hormone alone or in alternation with testosterone propionate in dosages as high as 500 mg. There was an average height increase above the normal increment of 15 per cent in those boys who received less than 20,000 I.U. or R.U., and of 36 per cent in those who received 20,000 or more units. The results in bone development are not consistent with those on height, as the lower dosage was associated with a greater rate of development (51 per cent above the normal increment) than was the case with

larger amounts (34 per cent above that of normal expectancy)

*Cryptorchidism and hypogonadism* The results of treatment in the 15 instances of cryptorchidism were a) the production of complete descent in 6 cases, b) partial in 6 and c), failure in 3. There was no correlation between the increase in body height and the descent of the testes as a) the greatest statural increase occurred in the boys in whom there was partial descent, b) less in those with complete descent and c), least in those with failure of descent. The difference in the height increase between the cases with complete descent and those which were failures was only 5.5 per cent.

There was, also, no correlation between the ad-

about 13 years. The external genitalia did not show a commensurate growth, the penis was that of a 10-year-old boy, the scrotum was small, pubic hair was present but the testes were still in the abdomen. This case illustrates the possibility of producing premature appearance of the bone development of puberty without, however, a) stunting the growth, b) affecting the descent of the testes, or c) producing closure of the epiphyses.

There was apparently no correlation between the effect on genital development and that on statural and bone growth. There was a slightly greater average increase in both height and bone age in those boys who showed effects of marked stimulation of the gonads than in those with moderate or slight effects,

TABLE 7. RELATIONSHIP OF AGE AT INITIATION OF TREATMENT TO RESULTS OBTAINED

| Age                | Number of Cases | Duration of Treatment | Average Amount of Hormones Given  | Percentage Increase in Height Above Normal Increment |  |            | Percentage Increase in Bone Age Above Normal Increment |  |            |
|--------------------|-----------------|-----------------------|---|--|--|------------|--|--|------------|
|                    |                 |                       |   | With chorionic gonadotropin                          | Chorionic gonadotropin and testosterone propionate | For series | Chorionic gonadotropin                                 | Chorionic gonadotropin and testosterone propionate | For series |
| Below 12 yr of age | 15              | 17.3 mo               | 29,956 R.U. or 1 U of chorionic gonadotropin 206 mg testosterone propionate | 21.6   | 31.4   | 36.2       | 45.2   | 49.7   | 47.7       |
| Above 12 yr of age | 5               | 13 mo                 | 18,450 R.U. or 1 U of chorionic gonadotropin 332 mg testosterone propionate | 34.5   | 98.6   | 73         | 15.0   | 44.3   | 32.6       |

vance in bone age and the effects on cryptorchidism since the greatest degree of growth acceleration occurred in those boys in whom there was failure of descent, there was less in those with partial descent and the least acceleration occurred in those with complete descent. This lack of correlation is exemplified in a boy of 8 years of age who, at the beginning of the period of treatment presented a picture of pronounced adiposogenital dystrophy with infantile genitalia and bilateral abdominal cryptorchidism (case 21). He was above the average height for his age but was retarded 18 months in bone development. Intermittent treatment with both chorionic gonadotropic hormone and testosterone propionate, thyroid substance by mouth and diet over a period of 3 years resulted in a loss of weight, an increase of 44 per cent above the normal increment in height and an advance of 116 per cent increase above the normal expectancy in bone development. The sesamoid bone appeared and the general bone picture was that of a boy at puberty of

but the differences were too small to be of any significance. There are marked variations between individual cases in each group.

The results in primary hypogonadism are exemplified in the case report.

#### CASE REPORT

*LE*, when first seen at the age of 10 years and 10 months, presented a tall and thin appearance, an almost infantile penis and small testes in an underdeveloped scrotum. His height was 67 inches, upper longitudinal measurement 31 in., lower longitudinal measurement 36 in., and span, 69 inches. He had never received endocrine therapy. He gave a history of having grown 9 inches in the previous 3 years, which was equivalent to 50 per cent increase above the normal increment for that period. He was given chorionic gonadotropic hormone parenterally in doses of 250 to 500 R.U. for 8 months and then testosterone propionate for the next 20 months. Treatment was discontinued when he was 13 years and 4 months old because of marked enlargement of the penis and testes,

and the appearance of secondary sex characteristics. He was 74¼ inches tall at the latter time, an increase of 7¼ inches, equivalent to a percentage increase of 38 per cent above the normal increment. After the cessation of treatment, the height increased at approximately the same rate of speed for the next 16 months and then slowed down to a normal rate during the following 6 months. He was 78½ inches tall at 15½ years.

The bone age was 1 year and 5 months, or 13 per cent, advanced above the normal bone age before treatment. After 28 months of therapy the bone development advanced 33 months, at a rate of 18 per cent above the normal increase. There was a spurt for 16 months after treatment was discontinued which was equivalent to an increase of 36 per cent above the normal increment; this was followed by a slowing down to a normal rate for the remainder of the period of observation. At 15½ years of age he had a bone age characteristic of 17 years.

Follow-up observations were made on 12 boys for periods varying from 6 months to 3 years after treatment was discontinued. All but one were 12 years of age or older at the time and subject to the same physiological spurt of growth of puberty. Growth continued in all, but at 3 different tempos: a), the rate was reduced in 7 boys who had shown an increase above the normal increment during treatment and in one boy who had had a diminished rate of growth; b), the rate was accelerated in 2 boys who had a normal growth increase and in 2 who had shown a lower-than-normal increment during treatment; and c), the rate was further reduced in one of the boys in the first group and in one of the boys in the second group after an initial acceleration.

These figures imply that in the majority of cases there is growth stimulation for the duration of treatment only, but that in a small percentage of cases growth may persist after treatment is discontinued. The accelerated rate may later be followed by a slowing down in growth.

The same tendencies were noted in bone development as evidenced by a decreased rate in 6 cases, an accelerated speed in 5 and no change in the growth tempo in one case; there was a subsequent diminished rate in 3 of the accelerated growth group. The rate of bone development eventually dropped from a height of 18 to 160 per cent above the normal increment to the normal or below the normal in 8 cases; it remained at about the same rate in 2 and was increased in 2. In one of the latter cases (*case 15*) an increase of 33 per cent above the normal increment during treatment was followed by an acceleration of 150 per cent above that of normal expectancy after treatment was discontinued. There was also a marked increase in height after treatment was stopped.

#### SUMMARY AND CONCLUSIONS

The effects of chorionic gonadotropic hormone and

testosterone propionate on the height and bone development were studied in 20 boys suffering from hypogonadism, hypogenitalism and cryptorchidism. The ages ranged from 8 to 15½ years with 15 boys below the age of 12 years and 5 above this age. The duration of treatment varied from 5 to 36 months.

The patients are divided into two groups: a), those who received chorionic gonadotropic hormone and b), those receiving chorionic gonadotropic hormone alternating with testosterone propionate. The average dosage for the first group was 28,380 R.U. or I.U. of chorionic gonadotropin and for the second group, 26,595 R.U. or I.U. of chorionic gonadotropic hormone and 475 mg. of testosterone propionate.

Every boy increased in height while under treatment, but in 3 different tempos: Fourteen grew at a rate greater than normal, 3 at the normal rate and 3 at a rate slower than normal. The average gain for the entire series was 32.2 per cent above the normal increment; it was greater in those receiving both hormones (47.9 per cent above the normal increment) than in those who obtained chorionic gonadotropic hormone alone (12.9 per cent above the normal increment). In the former group a greater increase in height was observed in those who received larger amounts of testosterone propionate.

The original height apparently had an influence on the results. Better results were obtained on the average, in those who were shorter than normal for their age at the beginning of treatment (56.2 per cent above the normal increment) than in those who were taller than normal (29.8 per cent increase above normal expectancy) or normal in height at the time treatment was begun (11 per cent increase above the normal rate). In spite of this increased rate of growth, the 3 boys who originally were retarded in growth at the beginning of treatment were still shorter than normal at the termination of treatment. In the group of boys originally taller than normal one was of normal height and all of the others were above after therapy. There was a slight increase in height in the boy who was of normal height at the time treatment was initiated.

The bone development progressed at a normal rate in 6 boys, at an accelerated rate in 14 and in no case was it below the normal. The average increase was 43.9 per cent above the normal increment for the series, 48.1 per cent for those boys who received both hormones and 39.7 per cent above the normal expectancy for those who received chorionic gonadotropic hormone alone. Here also, better results were obtained in patients with an initially retarded bone development (53 per cent above the normal increment) than in those with an originally normal (39 per cent increase above the normal) or an initially advanced bone age (38 per cent above the normal increment). At the termination of treatment, 1 case in the

originally retarded group showed an advanced bone age, 3 had a normal bone age and 3 were still retarded. In those with an initially normal bone age, 3 were advanced and 8 were normal. The 2 boys with advanced bone development at the start of treatment showed a still further advance at the termination of treatment.

The response in bone development was greater than that in height increase, but there was no constant relationship in the effect of treatments. On the basis of percentage increase, apparently, the greatest advance in bone age occurred in those individuals who were taller than normal and the greatest increase in height took place in those who were originally advanced in bone age. The next greatest increase is noted in those who were retarded in either bone development or height at the beginning of treatment. This would indicate that a greater stimulation is exerted in those individuals who are already advanced and in those who are retarded than in the individuals who are normal in either bone development or in height for their age.

The age at which treatment is instituted has an effect on the response in both height and bone development. Better results were obtained in height increase in boys above 12 years of age than in those below this age. This may be explained on the basis of added stimulation to the puberty spurt. The increase in bone development, however, was greater in those below 12 years than in those above this age.

Duration of treatment has an effect on the result in both height and bone age. There is an increasing percentage increase above the normal increment as the result of treatment for 6 months to 2 years, but not beyond this period. The results for shorter periods are not consistent.

There seems to be a relationship between the dosage and the effect on height, but not between dosage and the results in bone development. There is no relationship between the increase in height or the advance in bone development and the effect on the cryptorchidism and hypogonadism. It is possible to obtain a marked acceleration in bone age without an associated stunting of growth or beneficial effect on cryptorchidism.

Administration of large doses of chorionic gonadotropin hormone and of testosterone propionate to a boy of 11 years of age with eunuchoidism resulted in a slowing down of an increased rate of linear growth, but there was no cessation of height increase. There was also an acceleration of bone development, but no

closure of the epiphyses. Premature closure of the epiphyses was not observed in any boy in this series.

Follow-up observations on 12 boys showed that in the majority of cases the stimulative effect of chorionic gonadotropin hormone and of testosterone propionate on both height and bone development is present for the duration of treatment only, but that in a small percentage of cases accelerated growth may persist after the termination of treatment. This may be followed later by a slowing down in the rate of both height and bone growth.

We conclude that chorionic gonadotropin hormone and testosterone propionate have stimulating effects on height and bone development in prepubertal and adolescent boys. When both are given in successive courses of treatment they have a greater effect than chorionic gonadotropin alone, this is probably due to the action of testosterone propionate. In the dosages used in this series (250 to 500 R. U. or 1 U. of chorionic gonadotropin hormones and 10 to 25 mg. of testosterone propionate, over extended periods of time), there was not a single instance of premature closure of the epiphyses, or of stunting of growth. Both hormones, either alone or in combination, are valuable agents in the treatment of pre adolescent short stature.

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# Urinary 17-Ketosteroid Assays in Clinical Medicine<sup>1</sup>

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THE PRESENT COMMUNICATION surveys the practical usefulness of 17-ketosteroid assays in clinical medicine. In adhering strictly to this subject, many of the interesting and fundamentally important observations on the chemistry and physiology of the urinary 17-ketosteroids are not discussed. However, references to papers which give this type of information are given whenever possible.

## METHODS OF ASSAY

Because the usefulness of any laboratory determination depends upon its accuracy and availability a word concerning each of these aspects of assay is pertinent to our subject. Reliable evidence indicates that there are interfering chromogens in urine which, when present in large quantities, may give rise to errors in the commonly used colorimetric assay (Zimmerman reaction). Unless steps are taken to eliminate these errors, they lead to an overestimation of the 17-ketosteroid content. Fortunately, simple procedures for detecting the presence of and for eliminating most of the errors due to these interfering substances have provided reasonably reliable methods of determining the total 17-ketosteroid content of the urine (1-4).<sup>2</sup> In addition, procedures suitable for use in hospital laboratories are available for separating the total 17-ketosteroid of a single 24-hour urine specimen into alpha-alcoholic, beta-alcoholic and non-alcoholic fractions (5, 6).

## GENERAL SIGNIFICANCE

The evidence of today suggests that the urinary neutral 17-ketosteroids are excretory transformation products of certain adrenal cortical steroid hormones, and to a lesser extent of testicular steroid hormones (3, 7). Thus the 17-ketosteroid output may be con-

sidered to be proportional to, or a rough index of, the secretory activities of these two endocrine glands. However, because the secretory activities of the adrenal cortex and testes are influenced by anterior pituitary and thyroid hormones, the 17-ketosteroid assay may also give indirect information concerning their secretory activities. Thus, hypopituitarism and hypothyroidism, as well as hypofunction of the adrenals, may result in a marked lowering of the 17-ketosteroid output. Testicular deficiency results in a moderate decrease in output. On the other hand, hyperpituitarism and hyperthyroidism do not cause a significant elevation in 17-ketosteroid excretion. Indeed, in most instances abnormally high rates of excretion are associated with changes in adrenal cortical function or the presence of a testicular tumor. Theoretically, therefore, assay of urinary 17-ketosteroids excretion should provide information concerning certain aspects of adrenal, testicular, pituitary and thyroid function.

## NORMAL TOTAL URINARY 17-KETOSTEROID EXCRETION

Before the urinary excretion of 17-ketosteroids can be used as an index of either normal or abnormal endocrine function, normal standards of excretion, including the daily fluctuation, had to be established. Studies of the output of total 17-ketosteroids by normal individuals during consecutive 24-hour periods of time have shown that the output is not absolutely constant from day to day (8, 9, 10). However, the fluctuations which occur under normal circumstances are not great, the chances being two to one that a single assay will fall within 15 per cent of the 17-ketosteroid value obtained by averaging 30 or 40 consecutive daily assays. The normal fluctuations have not been explained and do not appear to bear any systematic relation to such phenomena as the menstrual cycle. It therefore appears that one or two *accurately timed and collected* 12-hour or 24-hour specimens of urine suffice for assays for most clinical diagnostic purposes.

<sup>1</sup> Such data of this paper as originated in this department are from studies aided by a grant from the Commonwealth Fund of New York.

<sup>2</sup> There is an error on page 211 of the paper listed as reference 4. On the second and third lines from the bottom of the page  $E_g:E_b$  should read  $E_b:E_g$ .

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In the left hand section of figure 1 representative measurements of the 17 ketosteroid excretion by normal children are plotted as the ordinate against their age as the abscissa. Values of 17 ketosteroids for adult women and men, respectively, are presented in the middle and right hand sections of the same figure. Average 17 ketosteroid values are represented by circles. The ranges in values are indicated by vertical lines running through the circles. The data are expressed in milligrams per 24 hours after applying corrections to eliminate over estimation due to in-

normal women are higher than the lowest values for normal men. The higher values in men may be explained by the fact that the testes contribute to the 17 ketosteroid output, whereas the ovaries of the women do not. It is also possible that this sex effect is due largely to differences in the adrenal cortical activity of men and women.

Although such measurements as are available on aged subjects are not directly comparable to those of figure 1, they suggest that the average 17 ketosteroid output falls during senescence (11, 12, 13).

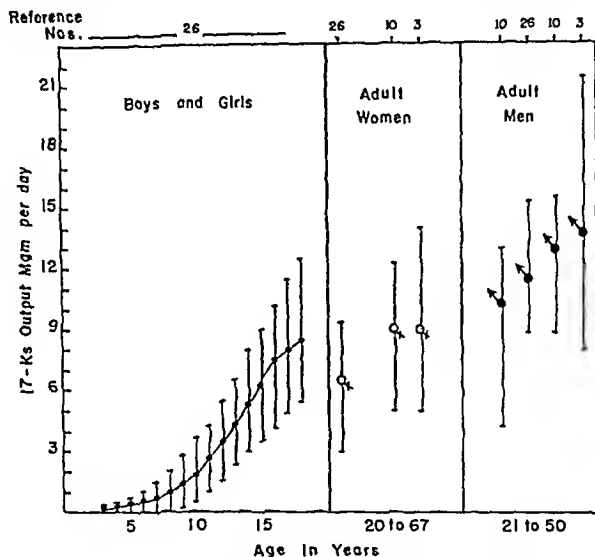


Fig. 1. 17 KETOSTEROID EXCRETION BY NORMAL SUBJECTS OF VARIOUS AGES

terfering urinary chromogens. Numerical references to the sources of these data are included at the top of the figure.

The solid curve running upwards from left to right through the average values for children shows that boys and girls excrete essentially no 17 ketosteroids from the time they are born until they are 7 or 8 years old. From then until they reach approximately 18 years of age the 17 ketosteroid excretion gradually increases to adult levels.

The average values for boys and girls of the same age are approximately equal. Men, however, have a higher average 17 ketosteroid output than women. It is not yet known at what age this sex difference becomes evident. The sex difference is not as clean cut as the age effect, since the highest values found for

#### TOTAL URINARY 17 KETOSTEROID EXCRETION IN ABNORMAL CONDITIONS

The establishment of preliminary normal standards of reference for individuals of varying ages and of the dependability of one or two determinations permits tentative appraisal of the urinary 17 ketosteroid excretion in various conditions in terms of normal, decreased or increased excretion. Table 1, lists according to the presenting symptom and sex of the patient, conditions in which 17 ketosteroid assays are of diagnostic value, together with the 17 ketosteroid excretion values found in each condition. There follows in the text a brief discussion presented according to the presenting symptom as given in the table. Numerical values have not been used for recording the 17 ketosteroid output because all of the values

reported in the literature are not directly comparable and because the normal 17-ketosteroid excretion is variable. Instead, plus and minus signs indicate whether the designated excretion tends to be abnormally high or low. A key to the significance of these signs is appended to the table.

Precocious or Abnormal Masculinization  
(Virilism)

This heading includes boys with masculine sexual precocity and women and girls with virilism. Experience has shown that it is often difficult to locate the exact cause of the complaint by history and physical

TABLE 1. 17-KETOSTEROID EXCRETION IN SELECTED CONDITIONS

| Presenting Symptom                                   | Causes (References are given in parentheses)                   | Sex     | Total 17-Ketosteroid Excretion <sup>1</sup> | Beta-alcoholic and Non-alcoholic 17-Ketosteroid Excretion <sup>1</sup> |
|--|--|---------|---|--|
| A Precocious or abnormal masculinization (Virilism)  | 1. Adrenal cortical carcinoma (3, 6, 7, 19 to 24)              | ♂ and ♀ | +++   | +++  |
|  | 2. Adrenal cortical hyperplasia (3, 22, 23, 24)                | ♂ and ♀ | ++ to +++                                   | o to +   |
|  | 3. Testicular interstitial cell tumor. (25) (one case)         | ♂       | +++   | ?  |
|  | 4. Central nervous system lesion (26)                          |         |   |  |
|  | Physiologic accelerated adolescence (26, 27)                   | ♂       | +   | o  |
| B Precocious or abnormal feminization (Gynecomastia) | 5. Ovarian arrhenoblastoma (3, 28)                             | ♀       | o   | o  |
|  | 1. Adrenal cortical carcinoma (29) (one case)                  | ♂       | ?+++  | +++  |
|  | 2. Ovarian granulosa cell tumor (30)                           | ♀       | o   |  |
|  | 3. Central nervous system lesion (3, 26, 28)                   |         |   |  |
|  | Physiologic accelerated adolescence (3, 26, 27, 28)            | ♀       | +   | o  |
| C Retarded Sexual Development or Hypogonadism        | 4. Associated skin pigmentation and bone cysts. (3) (one case) | ♀       | o   |  |
|  | 1. Hypopituitarism (3, 16, 26, 31, )                           | ♂ and ♀ | ≡   |  |
|  | 2. Hypothyroidism (3, 26)                                      | ♂ and ♀ | ≡   |  |
|  | 3. Castration  |         |   |  |
|  | Primary gonadal deficiency (3, 7, 13, 17, 32-35)               | ♂       | o to =                                      |  |
| D Dwarfism   | 4. Debility, malnutrition (3, 11, 16)                          | ♀       | o to -                                      |  |
|  | 1. Hypopituitarism (3, 16, 26)                                 | ♂ and ♀ | ≡   |  |
|  | 2. Hypothyroidism (3, 16, 28)                                  | ♂ and ♀ | ≡   |  |
|  | 3. Familial or non-endocrine (28)                              | ♂ and ♀ | o to -                                      |  |
|  | 4. Associated with anovarianism (3, 17)                        | ♀       | - to =                                      |  |
| E Overweight   | 1. Cushing's disease: (3, 20, 23, 24)                          | ♂ and ♀ | +++   | +++  |
|  | a. with adrenal cortical carcinoma                             |         | o to +                                      | o  |
|  | b. without adrenal cortical carcinoma                          |         | o to +                                      | o  |
|  | 2. Dietary plus constitutional factors (26) (children)         | ♂ and ♀ | ≡   |  |
|  | 3. Hypothyroidism (3)  | ♂ and ♀ |   |  |
| F Fatiguability and weakness                         | 1. Addison's Disease (3, 28, 32)                               | ♂       | - to =                                      |  |
|  | 2. Hypopituitarism (3, 16)                                     | ♀       | ≡   |  |
|  | 3. Hypothyroidism (3, 16, 28)                                  | ♂ and ♀ | ≡   |  |
|  | 4. Malnutrition (3, 11, 12, 13, 16)                            | ♂ and ♀ | ≡   |  |
|  | Anorexia nervosa   | ♂ and ♀ | o to =                                      |  |
|  | Chronic illness  |         |   |  |
|  | Non-endocrine carcinoma  |         |   |  |
|  | 5. Cushing's disease (see E 1 above)                           |         |   |  |

<sup>1</sup> Key to symbols: N, within normal limits; -, low normal or slightly below normal limits; =, definitely below normal limits, but more than 1 mg. per day, (applies only to subjects over 12 years old); ≡, very low: usually between 0.0 and 0.5 mg. and never over 1.0 mg. per day (application restricted to subjects over 12); +, elevated to correspond to average normal for older children or adults, (applies only to children); ++, moderately high: i.e. more than 6 mg. at 6 years, 10 mg. at 10 years, 15 mg. at 15 years, 18 mg. for adult women or 21 mg. for adult men; +++, Very high: more than 35 mg. per day.

A review of figure 1 shows that, while it is possible to detect an hypo-excretion of 17-ketosteroids by adults and older children, it is impossible to detect abnormally low values for children under 8 or 9 years. On the other hand, abnormally high values can be recognized easily in individuals of any age.

examination. Table 1 shows that the 17-ketosteroid measurement gives information which aids in determining the cause.

Males. In the male subject, a very high total 17-ketosteroid value indicates that there is either adrenal cortical carcinoma, adrenal cortical hyperplasia or

testicular interstitial cell tumor. Male patients with either of the two adrenal cortical diseases usually have testes which are of normal size for their age. In rare instances there may be enlargement of the testes due to the presence of aberrant adrenal cortical tissue. Testicular interstitial cell tumors, on the other hand, usually cause one of the testes to become abnormally enlarged. Thus, the chances are that a patient who is excreting very large quantities of 17 ketosteroids, but has normal appearing testes, has one of the two adrenal cortical diseases. These may be distinguished readily by determining the urinary excretion of the beta alcoholic and non alcoholic 17 ketosteroids. The rates of excretion of both fractions are very high in adrenal cortical carcinoma but are normal or only slightly elevated in adrenal cortical hyperplasia.

Sexual precocity in males associated with normal or slightly elevated 17 ketosteroid values is believed to be due to an increase in anterior pituitary secretory activity such as occurs normally at an older age. In boys, both testes are precociously enlarged and sperm may be demonstrable in the seminal fluids or by testicular biopsy. The increased pituitary activity may be due to central nervous system lesions such as pineal tumor, hydrocephalus or tumors of the floor of the third ventricle. These lesions may be very difficult to detect clinically. Therefore, one cannot always determine whether or not this type of precocity is pathologic.

**Females.** In virilized women and girls, a very high 17 ketosteroid excretion means that the patient has one of the two adrenal cortical diseases, while a normal or slightly elevated 17 ketosteroid output is suggestive of ovarian arrhenoblastoma. As in the male, only adrenal cortical carcinoma is characterized by a very high beta alcoholic and non alcoholic, as well as total 17 ketosteroid output.

Hirsutism is one of the characteristics of virilism in females. Patients with simple hirsutism tend to have a normal level of 17 ketosteroid excretion as do subjects with ovarian arrhenoblastoma. However, in simple hirsutism the clitoris is usually of normal size, whereas it tends to be markedly enlarged when there is an arrhenoblastoma.

#### Precocious or Abnormal Feminization (Gynecomastia)

This title includes girls with feminine sexual precocity and men or boys with gynecomastia. The girls show mammary development, but need not be having menstrual periods. Section B of table 1 gives a partial list of causes and the corresponding 17 ketosteroid output.

It is seen that the feminization due to adrenal cortical carcinoma is characterized by a very high 17

ketosteroid excretion. In other conditions associated with gynecomastia the 17 ketosteroid output is either normal or but slightly elevated.

In precociously developed girls, a normal or slightly high 17 ketosteroid value is consistent with either ovarian granulosa cell tumor or with accelerated adolescence secondary to increased anterior pituitary activity. As was the case in boys, the increase in pituitary function apparently may be spontaneous or may be related to a lesion of the central nervous system. If a pelvic or lower abdominal tumor can be felt, the chances are that one is dealing with an ovarian tumor. If the child has evidences of central nervous system disease, it is probable that the precocity is related to it. In most instances, in the absence of either of these conditions, the child represents one extreme of the normal variations in time of onset of adolescence.

#### Retarded Sexual Development or Hypogonadism

Section C of table 1 shows that patients with this complaint may be divided into groups characterized respectively by a) a 17 ketosteroid excretion level which is very abnormally low or b) a 17 ketosteroid excretion value which is normal or only moderately low. Very low values are almost always due to hypopituitarism or hypothyroidism. On the other hand, moderately low or normal values indicate that the complaint is due to some other cause, such as primary gonadal deficiency or debility not primarily of endocrine origin. When primary gonadal deficiency occurs without an associated pituitary or thyroid lack, large quantities of the gonadotropic hormones (FSH) may be demonstrable in the urine (3, 14).

#### Dwarfism

Retarded growth and retarded sexual development often occur together. When either of these disturbances is due to hypopituitarism or hypothyroidism, the 17 ketosteroid output tends to be very abnormally low (table 1, section D). There are usually fairly characteristic differences in the clinical appearance of patients with each of these diseases. The pituitary dwarf tends to have normal body proportions, to be mentally alert and to have smooth, fine textured skin. Occasionally these patients have symptoms of signs of an expanding intracranial lesion. The hypothyroid dwarf, on the other hand, tends to have short extremities, to be dull mentally and to have rough, coarse textured, cool, dry mottled skin. Measurements of the serum phosphatase and insulin sensitivity may help to distinguish between these two types of patients (15, 16). Their response to thyroid therapy also differs. While the thyroid dwarf responds satisfactorily to thyroid, the pituitary dwarf

responds poorly and may even develop symptoms of acute adrenal cortical insufficiency.<sup>3</sup>

A normal 17-ketosteroid excretion in a dwarfed patient essentially rules out the two foregoing diseases. Normal values have been observed in short but otherwise apparently normal children. Some of these have short siblings or parents; others are just beginning to grow rapidly.

Moderately low values have been observed in a group of moderately dwarfed girls who lack ovaries (3, 17). These girls fail to develop sexually and have a strongly positive urinary FSH test.

The 17-ketosteroid excretion in individuals whose growth and development is retarded because of congenital heart disease, chondrodystrophies, renal disease, chronic infection or malnutrition has not been studied adequately as yet.

### Overweight

Section E of table 1 presents the trend in 17-ketosteroid excretion by patients who are overweight from several designated causes. In Cushing's disease, the total as well as the beta-alcoholic and non-alcoholic 17-ketosteroid output tends to be very high if the subject has an adrenal cortical carcinoma, but tends to be essentially normal if there is no adrenal cancer. Patients with this disease complain of weakness (see below) and have osteoporosis, hypertension, atrophic skin and other signs which serve to distinguish them from most other types of overweight individuals.

In addition to certain patients with Cushing's disease, patients who are obese simply because they eat too much, or because they have a 'constitutional tendency' to become fat tend to have a normal or slightly increased 17-ketosteroid output. These patients are probably not suffering from hypopituitarism, hypothyroidism or hypoadrenocorticism, because any of these diseases will cause a marked lowering of the 17-ketosteroid output. It is seen that very low 17-ketosteroid values are observed in patient who are overweight because of myxedema. The myxedema may be due to simple hypothyroidism or may be an evidence of thyroid deficiency which is secondary to anterior pituitary deficiency.

### Fatigability and Weakness

The available information (table 1, section F) suggests that the 17-ketosteroid measurement is of value in distinguishing patients who complain of easy fatigability and weakness because they have a primary glandular deficiency from patients with diseases such as anorexia nervosa. Patients with Cushing's disease (see section E) have normal or high values. In

chronic illnesses from any cause there is a tendency for the 17-ketosteroid output to be moderately lowered. However, with the exception of male patients with Addison's disease, all patients with marked adrenal cortical, thyroid or pituitary deficiency tend to have still lower values which in most instances approximate zero. Equally low 17-ketosteroid values have been obtained in a patient who was having steatorrhea and was deficient in all of the fat soluble vitamins (18). Very low values are also encountered occasionally in patients with severe hepatic insufficiency (3). Because these latter two diseases have striking clinical characteristics, they should not be difficult to recognize.

### SUMMARY

The urinary 17-ketosteroid measurement has earned a place among those clinical laboratory procedures which provide diagnostic information. Determinations of the 17-ketosteroid output are particularly helpful in detecting hyperfunction and hypo-function of the adrenal cortex and hypo-function of the thyroid and pituitary glands.

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# Clinical Reviews in Andrologic Endocrinology

## III. Treatment of Seminal Failure

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IN A PRECEDING communication (1) the diagnosis and therapy of combined androgenic deficiency and seminal inadequacy were considered. However, deficiencies in seminal function are observed commonly in males who present no evidences of androgenic failure or other sexual incompetency as evaluated by present diagnostic criteria. Moreover it is unlikely that pronounced grades of hypogonadotropic failure exist in these patients for, if that were true, androgenic deficiency states would likewise be noted. The consideration of seminal inadequacy alone, therefore, assumes definite clinical importance.

Impairment of seminal function of the male, unaccompanied by androgenic failure, may be due to several factors: a) intrinsic testicular failure due to maldescent; b) extra-endocrine factors; c) altered metabolism due to thyroid disease; d) altered metabolism due to adrenal disease; e) inadequate gonadotropic activation of the germinal epithelium due to low-grade pituitary deficiency; and f) intrinsic germinal failure of the testes. Identification and evaluation of these various factors defines the therapeutic approach and, to a limited degree, determines the prognosis. The diagnosis and treatment of the first four classes of causes are relatively satisfactory; the diagnosis and therapy of the latter two classes, i.e., inadequate gonadotropic stimulation or intrinsic end-organ non-responsiveness, are unsatisfactory. In the preceding paper (1) a method for differentiating between these by therapeutic testing with gonadotropic preparations was outlined. The clinical data concerning these diverse etiologic factors will be considered briefly.

### SEMINAL FAILURE DUE TO CRYPTORCHIDISM

Therapy of cryptorchidism, either unilateral or bilateral, is indicated chiefly for three reasons. a). Inasmuch as the later stages of spermatogenesis are impaired in ectopic testes (2-8), deposition of the testes to the scrotum constitutes effective therapy of exist-

ing or anticipated sterility. b). Although some experimental evidence (9, 10) suggests no impairment of endocrine function of ectopic testes, most observers (11, 12) believe eventual reduction of endocrine function results from prolonged states of cryptorchidism. c). Recent studies (13) indicate that 11 per cent of all testicular tumors are found in retained testes, suggesting, therefore, a pertinent indication for deposition of ectopic testes to the scrotum in order to reduce trauma and to permit more satisfactory observation (14).

Prior to the onset of adolescence, there is little evidence that the histological pattern and physiology of undescended testes differs from that of scrotal testes (12); following adolescence, the undescended testes undergo progressive deterioration, the germinal function being involved first. Wangenstein (15-17) reported the non-existence of viable spermatozoa in the seminiferous tubules of undescended testes following adolescence. Weisman (12, 18) observed that sterility is a usual accompaniment of bilateral cryptorchidism. On the other hand, exhaustive surveys of the literature by Meyer (19) in 1927 and Rea (20) in 1939 revealed a number of instances in which motile spermatozoa were recovered from retained testes after adolescence and in which fertility was believed to be existent. Rawling (21) reported spermatogenic function in 10 of 27 cases of bilateral cryptorchidism. Uffreduzzi (22) observed spermatozoa in the testes of 10 per cent of his patients with cryptorchidism. Marechal, quoted by Wangenstein (15), observed the continuance of spermatogenesis in 50 instances of bilateral cryptorchidism. However, present knowledge (12) warrants the conclusion that the majority of cryptorchids is relatively sterile and that the degree of sterility advances with the number of years since adolescence.

The diagnosis of cryptorchidism includes the differentiation between migratory retraction of the testicle, known commonly as pseudocryptorchidism, and true retention. Doubtless, many enthusiastic reports concerning the efficacy of diverse therapeutic

measures or the existence of fertile states may have concerned instances of pseudocryptorchidism. Migratory testes do not require therapy and tend to remain permanently within the scrotum following adolescence.

Hamilton and Hubert (23) and Thompson and Heckel (24) have outlined the salient features of the differentiation between migratory testes and retained testes. Briefly, the technique of examination includes these procedures: a) a carefully taken history concerning scrotal development, b), a comprehensive knowledge of the pathologic anatomy of undescended testes, c), complete relaxation of the patient induced by reassurance, leisurely performed examinations, d), application of heat locally to those muscles in the scrotum and groin which cause retraction of the testicle, e), examination of the patient in the up right position, and f), repeated examinations on subsequent visits.

Considerable difference of opinion exists concerning the optimum time for institution of therapy, either endocrine or surgical, of cryptorchidism. Cabot (25) advocated endocrine therapy of cryptorchid patients between the ages of 3 and 7. Pleas for early therapy of cryptorchidism were advanced by Rubinstein (26), Nixon (27), Zelson (28), Sexton (29) and Thompson (30). On the other hand, Mumpress (31) delays therapy until the age of 10 believing that spontaneous descent would have occurred prior to that age, a view shared essentially by Weisman (12).

There are three modes of therapy for cryptorchidism: a) expectant treatment, b) endocrine therapy, and c) surgical procedures. These will be considered briefly.

### Expectant Treatment

Although it is conceded generally that in many cases retained testes will descend at adolescence, many observers (14) criticize the expectant management of cryptorchidism on the grounds that irreparable tubular damage of the ectopic testes resulting from increased thermal levels and trauma may develop prior to adolescence. Inasmuch as ample clinical evidence concerning the incidence of descent at adolescence is lacking in true cryptorchidism, final evaluation of the expectant treatment is not permitted (14).

### ENDOCRINE THERAPY

In this type of treatment one considers the employment of three forms of endocrine preparations: a) thyroid substance, b) gonadotropic preparations, and c) androgenic substances. Hamilton (14) believes endocrine preparations may effect descent only in those instances wherein relative hormonal deficiencies exist and in which no anatomical barrier to the progression of the testicle is existent. The use of endo-

crine therapy of cryptorchidism requires consideration of the following factors: evaluation of the functional status of cryptorchid testes prior to adolescence, appreciation of the pharmacological effects and limitations of diverse endocrine preparations administered for comparatively long periods of time, and the possible effects on scrotal structures which may alter the subsequent surgical status of the cryptorchid patient.

**Thyroid substance.** Prior to 1930, large doses of thyroid substance were employed enthusiastically for cryptorchidism. Although thyroid substance has been regarded by many conservative investigators as being capable of producing serious damage in adolescent patients, Engelbach (32) observed no deleterious effects from large doses of it in cryptorchidism. Recently, favorable reports on the use of small doses of thyroid substance in cryptorchidism have been submitted by Kreutzmann (33) and Meaker and Vose (34). Weisman (12) has found thyroid substance efficacious as supplemental therapy to gonadotropins in the treatment of cryptorchidism.

**Gonadotropins.** Since the initial report of Shapiro (35) in 1930 and the confirmation of his findings experimentally in monkeys by Engle (36) in 1932, many studies of the therapy of cryptorchidism with gonadotropins have appeared. The majority of these has been concerned with the therapeutic employment of three gonadotropins, chorionic, pituitary and equine. Critical evaluation of endocrine therapy of cryptorchidism by Thompson and Heckel (24) has revealed that one of five cases of retained testes may respond to this form of treatment.

Favorable responses to therapy of cryptorchidism with chorionic gonadotropin have been reported by many investigators (24-31, 37-89). In a comprehensive analysis of all published reports, Thompson and Heckel (24) in 1939 estimated that the rate of successful response was 61 per cent. This figure, however, was considerably higher than that from their own critical investigations. In a series of 28 patients less than 16 years of age, Thompson and Heckel induced descent in 9 of 33 cases of undescended testicles, a rate of 27 per cent. In 60 instances of cryptorchidism of all ages, they reported favorable responses in but 17 per cent, the lowered rate of successful outcome being explained in part by a more careful differentiation between migratory and retained testes.

The dosage of chorionic gonadotropin employed commonly varies from 100 to 500 R.U. injected daily or several times weekly. Bigler, Hardy and Scott (57) believe favorable responses will ensue from treatment with a total of 4000 R.U. of chorionic gonadotropin. Sexton (29, 66), Zelson (28) and Wilson (79) have noted successful descent following dosages of



5000 to 10,000 R.U. of chorionic gonadotropin injected over a period of 10 to 20 weeks. Careful observation to prevent the production of precocious maturity or excessive genital growth (24, 30, 64, 65) should be instituted and therapy discontinued if unfavorable responses are obtained. Although most observers (20, 30, 80-90) believe endocrine therapy of retained testes results in growth of scrotal structures favorable to subsequent surgical intervention, the recent studies of Eisenstaedt, Appel and Fraenkel (90) suggest that operative interference is rendered more difficult by preoperative endocrine therapy owing to the development of adhesions and to degeneration of the retained testes. Further investigation is necessary before conclusions concerning the status of chorionic gonadotropin in the therapy of cryptorchidism can be evaluated.

Pituitary gonadotropin has been employed in the therapy of cryptorchidism (29, 84). It has apparently no particular advantage over the chorionic gonadotropin. Available commercial preparations are lacking in potency comparable to the preparations of the chorionic gonadotropin.

Successful therapy of cryptorchidism with the equine gonadotropin has been reported recently by Kunstader (92). He believes the optimal dosage ranges from 50 to 100 (Cole-Saunders) R.U. intramuscularly 3 times weekly.

**Androgens.** Inasmuch as gonadotropic preparations doubtless exert some of their effects in the therapy of cryptorchidism by stimulating testicular secretion with subsequent development of the accessory sex organs, therapy of cryptorchidism with androgenic preparations has been investigated by Bauer and Koch (93), Hamilton and Hubert (94) and Zelson and Steinitz (95). Hamilton (14) concludes that results of androgenic therapy of cryptorchidism are discouraging and that gonadotropic preparations represent the treatment of choice whenever endocrine therapy is considered, a view shared by Talbot and Talbot (96), Thompson (30) and Weisman (12). Adequate data concerning the effects of androgenic substances upon spermatogenesis in the descended testicles are lacking.

In a comprehensive analysis of the present status of endocrine therapy of cryptorchidism, Thompson (30) has concluded that chorionic gonadotropin induces descent of those testes which would descend normally at adolescence, an opinion shared by Drake (97), Browne (98) and Johnson (99). However, Thompson (30) has advocated endocrine therapy of cryptorchidism for three reasons: a) Early endocrine therapy of cryptorchidism differentiates those cases due to hormonal deficiency and those due to anatomic barriers, identifying therefore, those patients who will require subsequent surgical intervention. b)

Endocrine therapy at an early age induces scrotal deposition of ectopic testes in 20 to 25 per cent of all patients, thereby, circumventing possible harmful effects of the prolonged ectopic location on gonadal function. c) Preoperative therapy with endocrine preparations facilitates surgical interference by stimulating growth and development of various scrotal structures.

**Surgery.** If endocrine therapy of cryptorchidism proves ineffective, surgical treatment is recommended by Denning (100), Duncan (101), Courtney and Duncan (102), Schuck (103), Turner (90), MacCollum (104), Wohl (105), Thompson (30), Hamilton (14) and others. The results concerning subsequent testicular growth and spermatogenic function following surgical therapy of ectopic testes are inconclusive (29, 106).

#### SEMINAL FAILURE DUE TO EXTRA-ENDOCRINE CAUSES

Attention to the diverse underlying extra-endocrine factors is a part of the rational therapy of seminal failure. This may include the correction of foci of infection; therapeusis of acute and chronic debilitating states; correction of anemic levels; therapy of metabolic disorders; correction of vitamin deficiencies; an adequate and well-balanced diet especially rich in lean meats and foods containing the essential amino acids; assurance of adequate physical activity; restriction of or abstinence from alcoholic beverages and tobacco; increased exposure to sunlight (107), avoidance of nervous strains and stresses; prolonged vacations, preferably of the out-door variety; and limitation of sexual activity, when it is relatively excessive.

#### SEMINAL FAILURE DUE TO THYROID DISEASE

When there are lowered basal metabolic levels, thyroid substance often proves to be effective therapy (33, 34). The explanation for the favorable response of hypothyroid patients to thyroid therapy is obscure. In a study of 53 male sterility patients, Hamblen, Pullen and Cuyler (108) observed that the seminal values, as judged by present diagnostic criteria, of patients with a moderately lowered basal metabolic rate were better than the seminal values of sterility patients in whom the basal metabolic rate was normal. Thyroid therapy may produce several desired effects: a) alterations in local tissue metabolism subsequent to improved oxygen metabolism; b) discharge of constitutionally improved spermatozoa; c) indirect effects on gonadotropic activation mediated via the pituitary gland; and d) direct alterations in thyro-gonadal relationships.

Medical and surgical therapy of hyperthyroid states may permit restoration of adequate seminal function.

## SEMINAL FAILURE DUE TO ADRENAL DISEASE

Alterations may occur in testicular function secondary to faulty electrolyte, water and glucose metabolism. The efficacy of cortical adrenal extract or desoxycorticosterone acetate in the therapy of this type of seminal failure has not been established. Recent experimental studies (109), however, have demonstrated that cortical adrenal extract may stimulate growth and subsequent spermatogenic activity in the testes of male rats.

Adrenogenitalism, resulting either from tumors or hyperplasia of the adrenal cortex, may impair spermatogenic function by a two fold mechanism: a) indirect alterations of the pituitary gonadal axis mediated via the pituitary, and b) germinal failure induced by the excessive androgenic substances. Surgical therapy of the adrenogenitalism may permit the return of normal spermatogenic activity.

## SEMINAL FAILURE DUE TO PITUITARY DEFICIENCY

Although the existence of seminal failure due to inadequate gonadotropic activation from the pituitary has been presumed from both experimental and clinical observations, factual proof that pituitary deficiency may induce seminal failure without concomitant androgenic failure is lacking. Diverse types of gonadotropic therapy have yielded varying results, the majority of which is disappointing.

*Chorionic gonadotropin.* Although the chorionic gonadotropin is assumed generally to activate chiefly the interstitial cells of the testes, favorable reports concerning its therapeutic employment in diverse grades of seminal failure have been submitted by Brosius and Schaffer (110), Charny (111), Heckel (112, 113) and Lloyd (114). In a group of 20 patients manifesting azoospermia, oligospermia and necrospermia treated with chorionic gonadotropin, Heckel (113) reported that pregnancies resulted in the wives of 4 patients. He concluded that therapy of seminal failure with the chorionic gonadotropin may influence favorably the number and viability of the spermatozoa. Valerio (115) observed striking improvement in a group of 25 men manifesting azoospermia following combined therapy with 5 cc. of whole pregnancy urine and 2 cc. of adrenal cortical extract thrice weekly for 2 months, although he did not state the incidence of resulting pregnancies. In a study of 6 normal men subjected to therapy with chorionic gonadotropin, Rubinstein (116) noted a pronounced increase in the spermatozoal count, although no alterations in the morphology, motility or viability of the spermatozoa were observed. On the other hand, McCahey (117), Kreutzmann (33), Weissman (12) and others have found the therapy of seminal failure with chorionic gonadotropin disappointing.

Experimental studies reveal equally conflicting conclusions concerning the activation of germinal epithelium with chorionic gonadotropin. Favorable responses with chorionic gonadotropin manifested by the proliferation of the germinal epithelium have been noted in the immature normal rat (118-124), but spermatogenic activity has neither been produced (120, 122, 125) nor augmented (118, 123, 124). On the other hand, spermatogenesis has been initiated by chorionic gonadotropin in the adult lizard (128) and the normal adult ground squirrel (129) during the non breeding season and in the immature lizard (128) and immature ground squirrel (129). Later studies (130) disclosed that spermatogenesis could be initiated and maintained by chorionic gonadotropin in both immature and adult hypophysectomized ground squirrels. The alterations in testicular structure which have been observed in both normal mature rats (124) and normal immature rats (125) following therapy with chorionic gonadotropin, are an increase in the weight of the testes, an enlargement and widening of the tubules and proliferation of the germinal epithelium without influencing spermatogenic activity.

*Pituitary gonadotropin.* The available commercial preparations of pituitary gonadotropin are lacking generally in potency comparable to the chorionic gonadotropin. Therapy with the pituitary gonadotropin yields results similar to those obtained by chorionic gonadotropin (113). Moench (131) reported varying degrees of improvement in spermatogenic activity in his group of patients treated with pituitary gonadotropin, a few of whom successfully impregnated their wives following therapy. Hotchkiss (132) observed considerable improvement in the seminal values of 3 patients treated with pituitary extracts and chorionic gonadotropin, 2 of whom subsequently were proven fertile.

*Follicle-stimulating gonadotropin from menopausal or castrate urine.* Improvement of spermatozoal morphology, count and motility in 9 of 10 men treated with follicle stimulating gonadotropin from menopausal or castrate urine was reported by Huberman, Israeloff and Hymowitz (140). However, no pregnancies resulted.

*Equine gonadotropin.* Clinical reports concerning the efficacy of equine gonadotropin in the therapy of seminal failure permit no definite conclusions. Rea (20) and Charny (141) have shown that equine gonadotropic therapy induces a normal histologic appearance of the testicle, in 3 of 5 patients treated, Charny (141) observed moderate improvement in the spermatozoal count. Employing equine gonadotropin, Looney (142) reported gradual restoration of seminal values in one patient manifesting oligospermia. Disappointing responses to therapy of seminal failure

with equine gonadotropin were observed by McCullagh and McGurl (143) and Kreutzmann (33).

*Pituitary 'synergist' and chorionic gonadotropin.* No detailed studies of the use of this combination therapy have been reported. A few patients, in our clinic, who had failed to respond to other gonadotropins have shown some improvement from the use of this type of therapy.

It is apparent, therefore, that gonadotropic therapy of seminal failure is at present disappointing. This may be due to *a*), the ineffectiveness of available commercial gonadotropic preparations; *b*), the infrequency of pituitary deficiency as a cause of impaired seminal function; and *c*), intrinsic testicular non-responsiveness, which cannot be evaluated by present diagnostic methods. If, in light of the above experiences, a trial of gonadotropic preparations for therapy of seminal inadequacy be considered, a suggested schedule has been outlined in the preceding paper (1).

#### SEMINAL FAILURE DUE TO INTRINSIC TESTICULAR INADEQUACY

Intrinsic testicular non-responsiveness may be due to diverse factors such as *a*) developmental inadequacy; *b*) local urologic disease; *c*) physiologic immaturity or senility; *d*) damage from roentgen-rays or radium; and *e*) alterations produced by surgery. Rational therapy for these states includes expectant treatment and institution of indicated urologic measures. Should these prove ineffective, the existence of a germinal failure must be accepted. The endocrine failure may be handled adequately by substitutional therapy.

Equivocal results have been reported concerning the value of androgenic preparations in the therapy of germinal failure of both man and the experimental animal. The *modus operandi* of this therapy is obscure but it may be related to a two-fold mechanism, *a*), the production of qualitative and quantitative alterations in the pituitary-gonadal axis mediated via the pituitary; and *b*), the occurrence of local alterations in testicular growth and development which may permit more adequate responsiveness to intrinsic gonadotropic activation.

The use of androgenic substances in experimental animals has produced confusing data, the majority of which cannot be correlated with human investigation. At an early stage in the study of the pharmacology of androgens, it was observed that administration of an extract of bull testes produced injury to the testicular tubules of immature rats (148, 149). Similar effects also have been noted from the administration of androsterone (150, 151), testosterone (152, 153) and testosterone propionate (152-156). These effects may be related either to depression of the gonadotropic fraction of the anterior pituitary by the androgenic

preparations (157) or to gonadal atrophy developing as a consequence of non-specific damage (158). Recent studies (159) in rats and mice indicate that small doses of testosterone propionate cause decreases in testicular weight while large doses have no such effect.

On the other hand, small doses of testosterone propionate administered to immature rats for a short period of time (5 micrograms daily for 10 days) are reported to have produced no testicular damage (160) but possible increases in weight (160, 161, 162), the explanation for the weight gain being related possibly to vascular congestion or to fluid increase concomitant with stimulation of the germinal epithelium (160).

Spermatogenesis has been initiated by androgens in the ground squirrel (129) and in the immature rat (163, 164). In instances in which spermatogenesis in immature rats had been inhibited by small doses of testosterone propionate, normal spermatogenic activity was resumed within 7 to 10 months following cessation of therapy (156) demonstrating that there was no permanent injury. It has been shown that administration of androgenic substances will maintain spermatogenesis in the hypophysectomized rat (11, 127-166), mouse (168) and rabbit (169) and that it will not accomplish this in the hypophysectomized guinea pig (170) and monkey (171). When injections of androgenic substances were delayed for 21 days postoperatively, failure to reinitiate spermatogenesis in the hypophysectomized rat (163) and mouse (168) was observed.

The production of oligospermia in a patient 67 years of age treated with daily subcutaneous injections of 10 to 25 mg. of testosterone propionate was observed by Heckel (172). Upon cessation of therapy, restoration of the spermatozoal count ensued, but it was depressed again upon resumption of therapy. Similar observations in 3 patients were reported by McCullagh and McGurl (173), the production of azoöspemia being noted in one patient. Although their follow-up studies (143) revealed no evidence of permanent damage to spermatogenesis, they advised caution in the therapy of seminal failure with androgenic preparations, noting that dosages of 25 mg. thrice weekly of testosterone propionate effected pronounced depression of the spermatozoal count. Decrease in the spermatozoal count ascribable to therapy with larger dosages of testosterone propionate has been observed likewise by Hamilton and Wolfe (174), Kenyon (185), Rubinstein and Kurland (160) and Heckel (176). Heckel and Steinmetz (177) observed no alterations in the volume of the seminal fluid in their group of patients treated with testosterone propionate. On the other hand, Rubinstein and Kurland (160) observed definite increase in the spermatozoal count of 5 normal men treated with 5 mg.

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# Endocrine Aspects of Mongolism

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WHEN, in 1886, Pierre Marie discovered the relationship between acromegaly and a 'dys-function' of the pituitary gland, he freed acromegaly from the concept prevalent in his day that the ancestors of the present generation were all giants, and that acromegaly represented an atavism—a retrogression to the giantism of early mankind. When Langdon Down (1), in 1866, published his classic paper on 'Ethnic Classification of Idiots' describing mongolism for the first time, he was influenced by that same dogma, and he was much concerned with the 'philosophical interest' attached to his observation because he felt that mongolism is 'an example of retrogression which furnishes some argument in favor of the unity of the human species'. While acromegaly has long been removed from the field of speculative mythology, mongolism still remains in that field, and relatively few sound attempts have been made to elucidate its fundamental nature. This is the more regrettable since the medical and economic importance of mongolism exceeds by far that of acromegaly. Whereas this latter disorder is rather rare, Bleyer has calculated the number of mongoloids in the United States to be at least twenty-eight thousand. One or two of each thousand newborn infants is a mongoloid.

Mongolism is characterized by a number of outstanding physical stigmata and invariably by a rather high degree of mental deficiency. So striking are these characteristics that anyone who is even slightly familiar with the disorder can select the mongoloid child out of hundreds of other mentally deficient children merely by casual inspection. It is not so much the famous epicanthal fold which characterizes the mongoloid child as it is his peculiar build, his head, his neck, his short extremities, and his heavy, long trunk. The general configuration suggests at sight the operation of abnormal endocrine factors in the genesis of the condition but some writers doubt the fundamental significance of the endocrine stigmata. They believe the cardinal feature to be the mental deficiency and such endocrine aber-

rations as exist to be secondary results of defects of the central nervous system.

This argument, however, is by no means compelling, since other types of idiocy and imbecility are not usually marked by evidences of hormonal defects. In a comparative postmortem study of 100 mentally deficient children, I found evidence that even in cases of severe malformations and gross defects of the brain, the function of the endocrine glands is surprisingly independent of anatomic lesions in the brain. The only exception is focal pathology of the surroundings of the third ventricle and the hypothalamus which causes a well defined endocrine disorder.

Mongolism is due to a prenatal developmental disorder which, unlike that of classic cretinism, is plainly evident at birth. Because of this fact, the study of the condition involves two different problems which are often confused in the literature. The antenatal developmental deficiency cannot depend on any endocrine organ or organ system of the embryo, because some of the malformations which are sometimes found to be associated with mongolism (septum defects of the heart, syndactyly, abnormalities of the hand lines, developmental deficiencies of the central nervous system) indicate pathological factors at work as early as in the second and third month of fetal life, at which period the endocrine system of the embryo has not yet developed. Thus the mongoloid deficiency is due either to a general germinal inferiority or to noxious agents within the maternal organism. That the latter possibility demands serious consideration is shown by the recent work of Benda, Dayton and Prouty (2), who have brought forth evidence that mongolism is correlated with an abnormal response to impregnation, the mother being at the threshold of hormonal sterility.

We may now examine, the second problem, the postnatal development of the mongoloid. Do the anomalies that are present at birth explain the abnormal course of development thereafter? The advocates of germinal inferiority say that the mongoloid is a different being, a unique 'species' due to an unknown whim of nature, a 'mutation' of the human

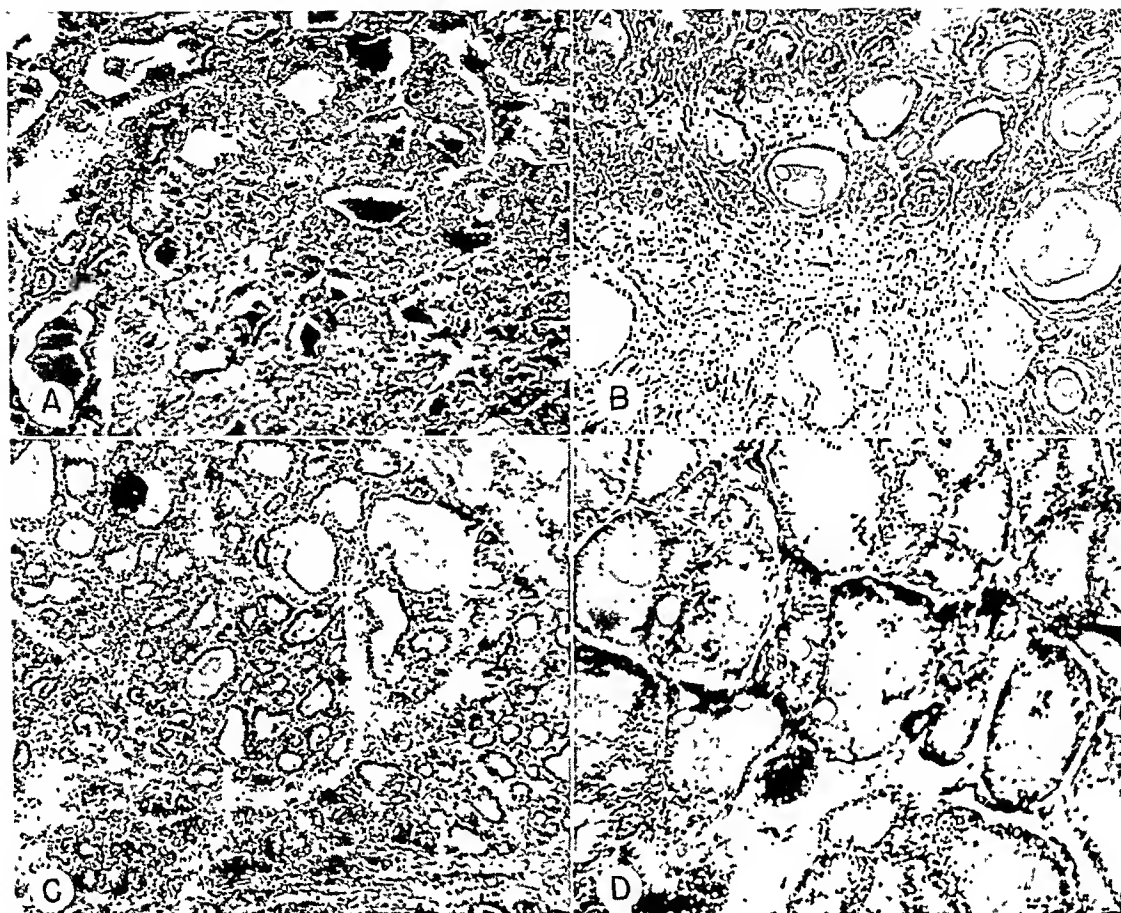


Fig. 2. THYROID IN MONGOLOID BABIES. A. THYROID of 2-month-old mongoloid male baby. Note irregular unfolding of follicles. Large areas are filled with microfollicular parenchyma without colloid, irregular cell growth and cell degeneration. Several follicles are enlarged, crowded and irregular in shape. They are filled with dark-staining, brittle colloid. Epithelium flat. B. THYROID of 9-month-old mongoloid baby. Marked fibrosis and degeneration of microfollicular parenchyma. Irregular unfolding of some follicles with colloid. Completely flattened epithelium.

C. THYROID of 9-day-old mongoloid baby. The microfollicular parenchyma is irregular and without colloid. Increased fibrosis. Some follicles distended with irregular shape and flattened epithelium. D. THYROID of 7-month-old mongoloid female baby, the youngest patient with a hypoplastic diffuse colloid goiter. All follicles distended to an average size of 250-350 microns. (Some had follicles of a size up to 500 microns.) All epithelial walls flattened. Follicles filled with brittle colloid. Interstitial tissue degenerated by compression. Colloid diffusion into spaces.

trophic. Menstruation is established in more than 50 per cent of the mongoloid girls, but the menarche is frequently delayed. Menstruation may cease entirely after several years.

Mongolism differs from cretinism with regard to the skin, subcutaneous tissue and the development of the skull and bones. The mongoloid skin is elastic and smooth, and the circulation is visible through the cutis. In some cases, myxedema develops secondarily. Many mongoloids show marmorated skin. The subcutaneous fat tissue is overdeveloped, but, at the same time, the musculature of the mongoloid is well developed and strong. The skull of the cretin is relatively large and the ossification is delayed. In mongolism, the appearance of ossification centers is not delayed, but they increase very slowly in size.

From a clinical point of view, we see in mongolism an immaturity of the development of the sex organs

with absence of the secondary sex characteristics. There is a tendency to obesity. There is general immaturity and retardation in growth with its early final cessation. The cartilage of the distal epiphyses degenerates, but there is definitely no premature ossification. Histologic studies show the presence of cartilage remnants after growth has ceased (4). The mongoloid patient, in short, shows numerous characteristics which parallel those of gonadal underdevelopment, adrenal cortical dysfunction, thyroid dysfunction and pituitary dysfunction; but the mongoloid deficiency does not fit precisely into any of the classical categories. It has been the purpose of a careful pathologic examination to throw some light on this complicated condition and to explain the peculiarities which distinguish this condition from those diseases which are better known.

Our pathological observations are based on a series



of 38 cases. Details of the pathology will be given in another publication, but the main observations may be summarized here.

Our thymus material is not sufficient to permit definite conclusions. This gland was hypoplastic in most of the cases with one exception—that of a 12-year old girl in whom it weighed 15.7 gm. The histologic examination did not reveal conspicuous anomalies in any case. We may, therefore, conclude that the thymus in mongolism is hypoplastic but that no consistent pathology is evident.

The adrenal in mongolism appears normal (5) in the first year of life, but after the lapse of that time, it shows a marked retardation of development of the outer cortical layers. These remain small, and the zona fasciculata especially is very narrow. In many cases, the reticularis covers a space larger than the two outer layers together. Conspicuous is the lack of lipid material in the zona fasciculata. The medulla appears to be well developed.

The gonads appear normal in young mongoloids. They show the same arrangement of Sertoli cells in the testicles as is seen in normal infants, with one or two germinal mother cells—so called 'male eggs' in each tubule. With the approach of puberty, immaturity of the testicles becomes conspicuous. In 7 cases of mongoloid males above the age of 15 years, the majority showed immature tubules tightly filled with Sertoli cells without spermatogenesis. In a few cases, primary spermatocytes were observed, but more progressive stages could not be found. There was one case only in which complete spermatogenesis was present. At the time of death, the boy appeared only slightly 'mongoloid' and there was considerable doubt as to the diagnosis. In his earlier years, however, the boy had shown several typical features of mongolism such as short, wrinkled hands, the prominent, flabby and underdeveloped ears, a pugy nose and flat face. This case is of importance when the question arises as to whether or not a mongoloid boy should be sterilized. Our autopsy material shows that the faculty of mongoloids to produce children is almost nil, but this one instance suggests that in so called borderline cases, maturation of the testicles may occur, and these cases need special consideration.

The ovaries of the mongoloid females appear normal in babies and young infants, but at the age of 8 to 10 years, they show a strong tendency to cystic degeneration, with destruction of the primary Graafian follicles. It is worth while to mention that the ovaries of some of the girls of 8 to 12 years showed an unusual number of atretic follicles and scars. The anatomic picture suggested almost a short phase of ovarian hyperactivity with subsequent exhaustion, and not a state of mere 'hypofunction'.

TABLE 1. CONTRAST OF CHARACTERISTICS OF ACROMEGALY AND MONGOLISM

| Acromegaly                                       | Acromicria Congenita (Mongolism)            |
|--|---|
| Increased growth of prominent parts (acromegaly) | Hypoplasia of prominent parts (acromicria)  |
| Increased pneumatization of skull                | Absence or underdevelopment of sinus system |
| Increase in diploe of flat bones                 | Underdevelopment of diploe                  |
| Increased cartilage activity                     | Decreased cartilage activity                |
| Splanchnomegaly                                  | Splanchnomicrocy                            |
| Gentomicrocy                                     | Gentomicrocy                                |
| Thyroid hypertrophy                              | Thyroid hypoplasia                          |
| Hypertrophy of adrenal cortex                    | Hypoplasia of outer cortical layers         |
| Hair abundant and thick                          | Hair scant and thin                         |
| Increased pigmentation                           | Lack of pigmentation                        |

The pathology of the thyroid is summarized in tables 2 and 3. In table 2, the weight of the thyroid is given in order to demonstrate the marked hypoplasia of this gland in mongolism. The hypoplasia is very impressive at autopsy. As a matter of fact, it is frequently difficult to find the thyroid in mongoloid children, and the recorded weight includes that of the capsule and connective tissue which could not be separated without microscopic dissection. The weights are, therefore, too high, but even so they indicate underdevelopment of the gland. There are very few careful observations on the weight of the thyroid of normal persons. For the adult thyroid, a weight of 20 to 30 gm. is considered normal, and for the newborn, a weight between 2 and 3 gm. is normal. I am not aware, however, of any data on the normal thyroid weight during infancy and childhood. Although it is stated that in feeble minded adults or

TABLE 2. WEIGHT OF THYROID IN MONGOLISM<sup>1</sup>

| Case Number | 1      | 2  | 3  | 4  | 5  | 6  | 7  | 8     | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17  | 18 | 19  | 20 | 21  | 22  | 23 | 24 |   |
|-------------|--------|----|----|----|----|----|----|-------|----|----|----|----|----|----|----|----|-----|----|-----|----|-----|-----|----|----|---|
| Age         | Months |    |    |    |    |    |    | Years |    |    |    |    |    |    |    |    |     |    |     |    |     |     |    |    |   |
|             | 15     | 2  | 5  | 6  | 7  | 7  | 10 | 45    | 57 | 88 | 98 | 10 | 12 | 14 | 15 | 16 | 16  | 17 | 17  | 18 | 20  | 20  | 28 | 31 |   |
| Sex         | F      | M  | M  | F  | M  | F  | M  | F     | F  | M  | F  | F  | F  | M  | M  | M  | M   | M  | M   | M  | M   | M   | M  | F  | M |
| Weight gm   | 10     | 23 | 11 | 05 | 25 | 20 | 20 | 10    | 50 | 25 | 45 | 98 | 90 | 70 | 60 | 77 | 110 | 50 | 110 | 35 | 230 | 190 | 55 | 3  |   |

<sup>1</sup> Including capsule and connective tissue



TABLE 3. MICROSCOPIC STRUCTURE OF THIRTY-FIVE MONGOLOID THYROIDS

| Case No. | Sex | Age    | Normal Epithelium, Normal Colloid Content | Struma Diffusa, Parenchymatosa | Struma Diffusa, Partly Micro-follicular, Partly Macro-follicular | Struma Colloidosa, Macro-follicular | Struma Lymphomatosa | Case No. | Sex | Age | Normal Epithelium, Normal Colloid Content | Struma Diffusa, Parenchymatosa | Struma Diffusa, Partly Micro-follicular, Partly Macro-follicular | Struma Colloidosa, Macro-follicular | Struma Lymphomatosa |
|----------|-----|--------|---|--------------------------------|--|-------------------------------------|---------------------|----------|-----|-----|---|--------------------------------|--|-------------------------------------|---------------------|
| 1        | F   | 2 days | +   |                                | +  |                                     |                     | 19       | F   | 9   |   |                                |  | +                                   |                     |
| 2        | F   | 9 days |   |                                | +  |                                     |                     | 20       | F   | 10  |   |                                |  | +                                   |                     |
| 3        | F   | 6 wk.  |   |                                | +  |                                     |                     | 21       | F   | 10  |   |                                |  | +                                   |                     |
| 4        | M   | 2½ mo. |   | +                              |  |                                     |                     | 22       | F   | 12  |   |                                |  | +                                   |                     |
| 5        | M   | 3 mo.  |   |                                | +  |                                     |                     | 23       | M   | 14  |   |                                | +  |                                     |                     |
| 6        | M   | 5 mo.  |   |                                | +  |                                     |                     | 24       | F   | 14  |   |                                | +  |                                     |                     |
| 7        | F   | 6 mo.  |   |                                | +  |                                     |                     | 25       | F   | 14  |   |                                |  | +                                   |                     |
| 8        | F   | 6 mo.  |   |                                | +  |                                     |                     | 26       | M   | 15  |   |                                |  | +                                   |                     |
| 9        | F   | 6 mo.  |   |                                | +  |                                     |                     | 27       | M   | 16  |   |                                | +  |                                     |                     |
| 10       | M   | 7 mo.  |   |                                |  | +                                   |                     | 28       | M   | 16  | +   |                                |  |                                     |                     |
| 11       | F   | 7 mo.  |   |                                |  | +                                   |                     | 29       | M   | 17  |   |                                | +  |                                     |                     |
| 12       | M   | 8 mo.  |   |                                | +  |                                     |                     | 30       | M   | 17  |   |                                |  | +                                   |                     |
| 13       | M   | 9 mo.  |   | +                              |  |                                     |                     | 31       | M   | 18  |   |                                |  | +                                   |                     |
| 14       | F   | 10 mo. |   |                                |  |                                     |                     | 32       | M   | 20  |   |                                |  |                                     | +                   |
| 15       | F   | 16 mo. |   |                                |  | +                                   |                     | 33       | M   | 20  |   |                                | +  |                                     |                     |
| 16       | F   | 18 mo. |   |                                | +  |                                     |                     | 34       | F   | 28  |   |                                | +  |                                     |                     |
| 17       | F   | 4½ yr. |   |                                | +  |                                     |                     | 35       | M   | 31  |   |                                |  | +                                   |                     |
| 18       | M   | 9 yr.  |   |                                |  | +                                   |                     |          |     |     |   |                                |  |                                     |                     |

children, the thyroid is frequently underdeveloped, I found it useful to check this statement and to compare the mongoloid thyroid with that of undifferentiated idiots and imbeciles of various sorts. Forty cases were available in which the thyroid was removed and the weight determined under exactly the same circumstances as in the mongoloid autopsies. The results are given in the table 4. Although the values given may be too low for normal children, they prove beyond doubt two facts, a) that the thyroid is usually not extremely hypoplastic in uncomplicated idiocy and imbecility, but that it corresponds to a low normal; and b), the thyroid of monogoloids is extremely hypoplastic when compared with that of other mentally deficient children. Measurements demonstrate that the hypoplasia varies in its extent, but that it was found in all cases with the exception of two, which will be discussed later. The most extreme degrees of hypoplasia were seen in 4 patients. One mongoloid girl of 4.5 years of age had only 2 small nodules of thyroid tissue with a total weight of 1 gm. on each side of the trachea without an isthmus. In one mongoloid baby the thyroid was absent but some thyroid tissue was found within the thymus. One 9-year-old boy had a thyroid weighing 2.5 gm. and in one 18-year-old boy the gland weighed 3.5 gm. I might mention that in several cases, the thymus and the thyroid were connected with each other, and it was impossible to separate the two without the use of the microscope.

A real understanding of the thyroid pathology is to be gained only through microscopic study. The observations are tabulated in table 3. The terminology used is the same as that used by De Quervain and collaborators (6) and especially Wydler (7). These outstanding Swiss scholars have studied cretinism on the basis of the large material from the canton of

Berne. The paper represents the rather authoritative opinion of a large group of Swiss scholars in regard to cretinism. Table 3 shows that the most frequent finding in the thyroid of mongoloid children and adults is a diffuse hypoplastic colloid struma. The histology is given in illustrations (fig. 3, A, B, C). These glands show a uniform picture of enlarged follicles measuring 250 to 500 microns, filled with a colloid which stains dark red or blue; the epithelial walls are flattened; the interstitial tissue has disappeared, and the follicles touch each other. This simple picture of a hypoplastic colloid thyroid was present in all mongoloid girls and in 6 boys. The youngest patients with this type of colloid struma were 2 babies of 7 months. During the first year of life the most frequent picture, however, is a small hypoplastic gland, the periphery of which shows follicles distended with heavy staining colloid and having flattened epithelial walls. The central portion of these thyroid glands shows an increase in connective tissue and an accumulation of small distorted follicles of various size without colloid. The atelectasis of the central nodules is different from the normal infantile thyroid in that the stroma

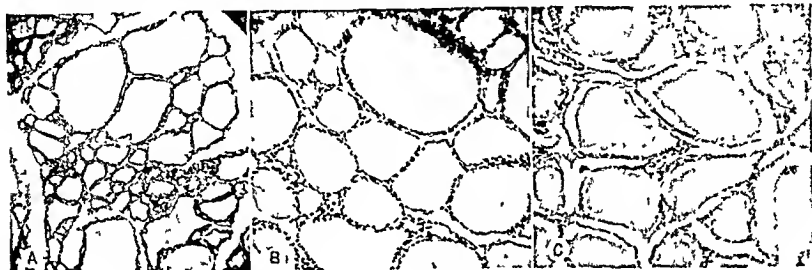
TABLE 4. AVERAGE WEIGHT OF THYROID OF 40 CONTROL INDIVIDUALS<sup>1</sup>

| Age in Years | Thyroid Weight gm. |
|--------------|--------------------|
| 2-5          | 2-4.5              |
| 8            | 6                  |
| 12           | 8-14               |
| 14           | 12-14              |
| 15           | 12-20              |
| 19           | 17-24              |
| 20           | 12-27.5            |
| and above    |                    |

<sup>1</sup> Cases of mental deficiency chiefly idiots and imbeciles.

is greatly increased, and the epithelium (parenchyma) shows an irregular proliferation of cells with pycnosis and absence of normal follicle formation. It seems, however, that as time goes on, the atelectatic nodules disappear and are replaced by simple colloid accumulations. In 3 babies, the thyroid was degenerated and did not show colloid formation. In the youngest and smallest baby, that of two days, the thyroid showed unusually high epithelial walls and a periphery with distended follicles containing rather dark colloid. This thyroid was somewhat advanced in its development rather than retarded.

of colloid and that only in a small percentage of cases is colloid to be found at all, if present, it is rather brittle. As Wyder (7) emphasizes, if colloid is present, it is sparse and indicates a previous state of functional activity. These observations refer to the thyroid struma of endemic cretinism. In myxedema and sporadic athyroidism, the thyroid is atrophic or missing, and is not functioning at all. The changes are described by Marine and Lenhard (9) as follows: "The colloid is practically absent. The epithelial cells have lost their regular and columnar type and are irregular in size and shape. The nuclei are in general



F - T  
A  
B  
C  
diffusion into spaces

FOLLICULAR COLLOID GOITER IN 28-year-old female  
resting  
Note extreme flattening of epithelium and colloid

#### DISCUSSION

The material presented herein proves beyond doubt that mongolism is associated with thyroid pathology. This fact has been suspected for more than 40 years, and yet, no progress has been made in understanding the mongoloid pathology because a discussion of thyroid pathology in mongolism was blocked through the observation that mongolism has nothing in common with cretinism. When the pathology of the mongoloid thyroid was emphasized, the exponents were silenced on the basis that the differences between cretinism and mongolism are obvious, and that biochemical and metabolic studies on mongoloids have so far failed to demonstrate the thyroid pathology. It is, therefore, necessary to discuss the differences between cretinism and mongolism to some extent. As a matter of fact, it is this difference between the two conditions which will greatly enlarge our general understanding of the various types of thyroid pathology. The histology of the thyroid in cretinism is characterized by degeneration of the parenchyma, proliferation of the connective tissue stroma, degeneration and insufficiency of the blood supply, and a deficiency or complete lack, of colloid. It should be emphasized that the cretin struma is free

large, often hyperchromatic, and irregular in size and outline. Nuclear figures are still observed but the new formation of cells is not sufficient to offset the cell death and the follicles become smaller. The surrounding fibrous stroma is relatively—perhaps absolutely—increased as the follicles become smaller from the death of their secreting cells. Although the amount of cell death, degeneration, and fibrosis may vary from case to case, the common denominator of all functional inadequacies is the loss of the ability of the follicles to form and store colloid.

In contrast to the thyroid pathology of cretinism and myxedema, the thyroid of the mongoloid is essentially a colloid struma. The thyroid of the mongoloid has the ability to secrete and store colloid, and it is because of this faculty that all biochemical and metabolic studies in mongolism have failed to demonstrate a marked thyroid deficiency. The colloid thyroid (goiter) is anatomically abnormal (9), but conclusions with respect to the function of such thyroids are not justified. They may be 'hyperthyroid,' 'euthyroid,' or 'hypothyroid.' The functional ability of a thyroid can be determined only by biochemical and metabolic studies on the patient. Such studies have been reported by Bend and Bixby (10 in 1939). In

this paper, Bixby reported blood cholesterol values in 50 persons with mongolism, who ranged in age from 2 to 29 years. The values ranged from 135 to 234 mg. per 100 cc., values now accepted as normal. Five of the values (which were those of females) were close to 250 mg., which is a high normal level. One boy of 10 years had on 3 different occasions, values of 312, 291, and 244 mg., respectively. The basal metabolic rates of persons with mongolism were studied in 25 cases, and it was shown that if the Mayo standards are used, all mongoloids had values between  $-2$  and  $-24$ , the majority being between  $-10$  and  $-20$ . If the Talbot weight standard is used, the majority still showed values ranging between  $-1$  and  $-21$ , with the exception of 4 cases who showed low plus values; with the Talbot height standard, the majority were between 0 and  $-10$ . From these biochemical studies, the conclusion may be drawn that the function of the thyroid, as far as basal metabolism and iodine metabolism are concerned, is within normal range in mongolism; but the metabolism is 10 to 20 per cent below the average. The hypoplasia of the thyroid, as well as these metabolic studies, discard the assumption that hyperthyroidism might be considered.

While in cretinism, the thyroid has lost its ability to store and secrete colloid and there is degeneration of its secretory apparatus, the thyroid of mongoloids has a well-preserved functional ability but is a 'resting colloid thyroid (goiter).' Knowledge of the mechanism of colloid goiter has been gained recently through many experimental studies on hypophysectomy. Van Dyke (11) summarizes the morphologic changes in the thyroid after hypophysectomy. 'Undischarged colloid accumulation in vesicles lined by flat, inactive epithelial cells.' Salter (12) describes the functional effect of hypophysectomy as follows: 'The basal metabolism falls to 80 per cent of normal, but the organism stops short of clinical myxedema.' This drop of the metabolic rate 'short of myxedema' is exactly what is present in the majority of mongoloid persons, with the exception of a few who develop a real myxedema which is easily mitigated by thyroid therapy. The accumulation of colloid, with a flattening of the follicle walls, and the general hypoplasia indicate, therefore, the lack of stimulation by the thyrotropic hormone of hypophyseal origin. While cretinism is the result of a primary degeneration of the thyroid, which can not react to thyrotropic hormones even when given in excess, the thyroid of the mongoloid child is primarily a normal thyroid which lacks functional stimulation from the pituitary. The thyroid of the mongoloid is essentially identical with the thyroid of the experimentally hypophysectomized animal.

We are, therefore, able to conclude that the endo-

crine pathology of mongolism is characterized by a), hypoplasia of the thyroid with a resting colloid goiter; b), by failure of the gonads to mature; and c), by a hypoplasia of the adrenal cortex in which the outer layers fail to develop normally and to store lipid in the zona fasciculata. In all three organs the glandular pathology arises secondarily, due to the lack of stimulation and not to a primary anomaly or disease.

The endocrine pathology in mongolism indicates a functional pathology of the pituitary gland. The question arises as to how much of this functional disorder is the result of anatomic changes of the anterior lobe of the hypophysis.

The number of the specific physiologic effects of the anterior lobe of the pituitary is remarkable, and Collip (13) cites 16 of these specific actions. The cytologists and pathologists have generally recognized only 3 cell types of the anterior lobe, i.e., the chromophobes, the alpha and the beta cells. Some anatomists have expressed the opinion that the chromophobes, are 'reserve' cells which have no secretory action. This would leave the whole secretory activity of producing at least 16 different effects to the two cell types, the alpha and beta cells.

The only known anatomic patterns of pituitary pathology are acromegaly, Simmonds' disease and pituitary basophilism, the first being associated with an eosinophilic (alpha cell) adenoma; the second with destruction of all cell elements and the third with an increased number of basophilic (beta) cells. It has been concluded that the eosinophilic cells produce 'growth hormones.' It is beyond the limit of this paper to discuss the conclusiveness of this claim. There are several facts which are not yet settled, but even if we accept the conclusion, that the eosinophilic elements have some relationship to the clinical phenomenon 'growth,' there is no doubt that the relationship between the anatomy of the gland and its physiologic activity is far more complicated.

Experimental pathology has dwelt to a great extent on the relationship between the pituitary and the gonads. There is much experimental evidence that the pituitary reacts to castration with the formation of vacuolated beta cells known as 'castration' cells. Severinghaus (14) draws the conclusion that the data at hand 'tend further to bring the basophils into direct relation to the gonads.'

The effect of thyroidectomy on the pituitary cells seems to vary with the experimental animal species. In some animals, an increase in the number of basophils has been observed with the development of vacuolation similar in appearance to that following castration. For man, it seems more probable that the alpha cells are increased in hypofunction of the thyroid. Erdheim (15) has reported a marked increase of alpha-cells in congenital thyroid hypoplasia.

At present it is safe to conclude that pathology of pituitary function may manifest itself in some anatomic changes, but it is impossible to draw direct conclusions from the anatomy of the pituitary body as to the physiologic potency of its secretory elements. A deficiency may manifest itself in the absence of some cell elements, but a dysfunction in which there is potency of some factors and inadequacy of others can hardly be expected to manifest itself in such simple patterns as the varying distribution of three main cell types, which are concerned with more than 16 different physiologic actions.

With this in mind, it is not surprising that the antithesis of acromegaly, congenital 'acromicry' is not associated with a decrease or absence of eosinophilic elements in cases of congenital acromicry. Almost the opposite is true. In 1939, (16) I published a first report on the pituitary gland in 16 cases of mongolism, and demonstrated that the majority showed an increase in eosinophilic elements. The present report is based on observations of 32 pituitaries in mongolism. The results are shown in table 5. The data confirm in part the former report of a marked increase in alpha cells in mongolism, and establish the fact that pituitary pathology in mongolism is not a uniform histologic picture which can be considered characteristic of that condition.

Histologically, the pituitary gland in mongolism may be one of two main types. The most common is characterized by an increase in alpha cells which occupy the whole field or fill large areas to the exclusion of the other cell types (15 cases). In 4 additional cases, a rather similar picture was found, but there were many beta cells also (one-third to two thirds of all cells), these occurred in groups or islands, and showed distinct vacuolation with halo formation around the nuclei, resembling castration cells. This cell type was found in boys above the age of 9 years. The pituitary from the one female, aged 28, also showed an increase in the number of beta cells. Nineteen of 32 cases of mongolism showed, therefore, a predominance of chromophilic elements with almost no chromophobic cells. The second histologic type of pituitary was characterized by a prevalence of chromophobes with only a few other cell types present, one had alpha cells and 3 beta cells, respectively. In 3 cases, the distribution of the various cell elements appeared not unusual.

These observations seem confusing, but if one bears in mind that these patients suffer from the residuals of an early developmental disorder, it is readily understood that the histology of the pituitary not only reflects the pathology, but reflects the varying adjustment of the pituitary to its endocrine surroundings, at the same time. The pathology is indicated by the shift of the pituitary cell types to

ward the eosinophils and the lack of other types of cells in these glands. In the other group of cases, the general deficiency of the chromophilic cell types is conspicuous.

There are several ways of interpreting these findings. If the assumption is made that the alpha cells are related to the production of the growth factor, and if Erdheim's (15) suggestion that the presence of increased alpha cells in aplasia of the thyroid means a compensatory activity of the pituitary is considered, then, the most reasonable interpretation of our observations would be, that in the majority of cases of mongolism, the pituitary is attempting to compensate for the deficiency of the thyroid and is able to produce

TABLE 5 PITUITARY IN MONGOLISM

| Histology of Anterior Pituitary Lobe                                      | Number of Cases |
|---|-----------------|
| Chromophobes predominant, only few other cells present                    | 6               |
| Chromophobes predominant, scattered alpha cells present                   | 1               |
| Chromophobes predominant, scattered beta cells                            | 3               |
| Alpha cells predominant, almost no other cells                            | 15              |
| Beta cells predominant or numerous, castration cells, alpha cells present | 4               |
| Fair amount of all cell types   | 3               |
| Total   | 32              |

a fair amount of growth hormones which keep the children growing for about 10 to 12 years. In some cases, there is even a hyperfunction, in which ensuing acromegalic traces are recognizable. In another group of 10 cases, the secretory ability of the pituitary appeared diminished and a state of general pituitary deficiency was suggested by the anatomic observations.

If this interpretation is accepted, it is necessary to assume that the growth stimulating capacity of the pituitary is intact, but that the responsiveness of the thyroid, adrenals, and gonads is at fault. It is, however, probable that the eosinophilic reaction in the majority of the pituitary cells does not indicate that these cells are producing growth-promoting hormones. The fact that an increase of alpha cells has been observed experimentally in hyperthyroidism and hypothyroidism and after castration, seems to indicate that the staining reaction is rather unspecific and manifests only a shift in the endocrine balance.

Whatever the final interpretation may be, the material presented indicates that the pituitary in mongolism is in a state of dysfunction which is the center of the disorganization of the endocrine environment of the mongoloid person.

## CONCLUSIONS

On the basis of previous clinical studies and the autopsy material of the 38 cases presented in this report it seems possible for the first time to offer a definition of mongoloid deficiency. As a result of a pathologic gestation period, which either is lacking in some essential hormonal agents or is pathologic due to noxious metabolic factors, the mongoloid baby is essentially immature at birth ('unfinished child'). As a result of the immaturity, the pituitary and thyroid of the mongoloid baby are not able to function properly and to adjust to the conditions of postnatal life. It seems probable that the noxious metabolism damaged the thyroid and pituitary of the baby; this is indicated by the atelectasis and fibrosis of the thyroid and necrosis of most of the pituitary cells which is seen in mongoloid babies. The failure of proper development during the first year is due to the inability of these key glands to function. The dysfunction of the pituitary results eventually in a hypoplastic colloid goiter of the thyroid and in failure of the adrenal cortex to develop normally. The lack of gonadotropic stimulation results further in degeneration and immaturity of the gonads of both sexes. The fact that the mongoloid baby after the first year of life starts to grow and to develop fairly normally for about 10 years is explained through the activity of the pituitary, which appears to develop a capacity for at least a part of its functions. Not before the approach of puberty, which creates new requirements on the endocrine environment of the mongoloid child, does the inadequacy of the pituitary become conspicuous again. At that time, obesity or cachexia occur, and, as the data indicate, the majority of mongoloid patients die in the second decade of life, if they have survived the first year.

The pathology of mongolism is of great importance because of the question as to whether therapy has a reasonable chance of improving the condition of these unfortunate children. Since mongolism is essentially a prenatal deficiency, the main purpose should be to recognize the condition during prenatal care. The paper of Benda, Dayton, and Prouty (2) seems to provide some material which suggests that this goal is not entirely out of reach. At present the best chance to treat the mongoloid is as shortly after birth as possible. Our studies on the mongoloid brain suggest that edema of nerve cells and metabolic changes of the white matter produce early degeneration of the brain, and these changes are not reversible after the lapse of some months. An early treatment will be successful, however, only in a certain percentage of cases. The prognosis of treatment depends on the degree of retardation at birth and the amount of congenital malformations present. The greater the number of malformations such as syndactyly, septum

defects of the heart, congenital cataracts, or signs indicative of developmental disorders of the brain and spinal cord, the less favorable the prognosis. On the other hand, some mongoloid babies show only a few markings of retardation, and in these cases, the prognosis is better. Although there are a few encouraging reports in the literature on thyroid and pituitary therapy in the mongoloid, therapy is still in an experimental state, and our pathologic study indicates the complexity of the situation with which the clinician has to cope.

DeQuervain (6) has pointed out, for cretinism, that if only the most extreme cases are seen, the problem appears simple and uniform, but if there is opportunity to observe cretins by the dozen and hundreds, ranging in degree from creatures below the level of animals up to somewhat simple citizens who are able to vote, and involving all the variations between dwarfism and normal growth, then the problem appears extremely complicated, and one is inclined to ask what is the common denominator for all of these conditions. This is also true for mongolism. As long as a physician is familiar with only a few marked cases and the literature is based on the study of a few case reports, the problem appears simple. The statement may be heard that mongolism is present or is not present and intermediary stages are unknown. Those, however, who have had the opportunity to study mongoloid persons by the hundreds, and autopsies by the dozens, will agree that mongolism is as variable as cretinism, and all shades of this condition may be observed from the most extreme developmental disorder with idiocy, spinal dysraphism, heart defects, syndactyly, and congenital cataracts, to a borderline condition with an I. Q. of 50. It is my conviction that what has been done in one or two generations for the improvement of cretinism may also be done and is possible for mongolism.

## SUMMARY

1. The endocrine aspects of mongolism encompass two separate problems which are frequently confused; mongolism as a prenatal developmental disorder cannot be caused by an endocrine disorder of the mongoloid baby. Mongolism is due either to noxious factors within the mother (endocrine disorder of the mother) or to a genetic inferiority of the germ plasm. The second problem is concerned with the pathology of postnatal development. Is this the result of an abnormal constitution of the child or a dysfunction of its endocrine system? The present study deals with this aspect only.

2. Persons with mongolism show a number of features indicating an endocrine disorder, in contrast to the physical development in other types of mental deficiency. The symptoms of mongolism include,

among others a) Retardation of bone growth, while the time of appearance of ossification centers is about normal. The result is stunted growth or dwarfism and acromicria b) Pathology of gonadal development with lack of sex differentiation, lack of development of secondary sex characteristics and sexual immaturity c) General infantilism with tendency to obesity or general cachexia d) Infantilism of the vascular system

3 An analysis of the material of 38 autopsies provides the following evidence a) The gonads of mongoloid babies were normal, but those of mongoloid children and adults were immature and showed degeneration b) Adrenal medulla and cortex were normal shortly after birth, but in older cases, the cortex had failed to develop normally and remained small. The two outer layers were especially involved, the zona fasciculata was narrow and without the usual lipid content c) The thyroid was hypoplastic in all cases. The two seeming exceptions (case 21 and 22, table 2) had a lymphadenoid goiter and a colloid goiter, respectively. Microscopic examination of the thyroid after birth revealed large areas of microfollicular parenchyma without colloid and irregular fibrosis. After about 7 months of life, the most common picture was a hypoplastic colloid goiter. In 13 instances the colloid goiter was macrofollicular. In 16 instances, there were macrofollicular areas with much colloid besides microfollicular areas with little or no colloid d) The pituitary in mongolism showed a strong tendency to an increase of eosinophilic cells of the anterior lobe. Fifteen cases showed predominance of alpha cells. In 4 cases, beta cells were present besides alpha cells, most of the beta cells being castration cells. In 10 instances, the pituitary showed predominantly chromophobic elements, with frequent necrosis and little or no formation of chromophilic elements. In 3 instances, the pituitary appeared not unusual. The pituitary of the female mongoloid showed a tendency to accumulate brittle colloid, which fills and frequently distends the whole cleft with resulting compression of the anterior lobe. In contrast to the pituitary of the female, colloid was absent in the pituitary of the male with the exception of one case

4 These observations explain why previous investigators, whose conclusions were based for the most part on a few case reports, have arrived at contradictory conclusions. A survey of the whole of our own material, as well as that reported in the literature, shows a surprising uniformity of observations, if age and sex of patients are given due consideration

5 The material at hand furnished conclusive evidence that mongolism is not associated with a primary congenital pathology of the adrenal, but is associated with a secondary pathology of the adrenal

cortex, consisting of hypoplasia of the outer layers and lack of lipid formation. It is suggested that this functional pathology is due to a lack of stimulation by the corticotrophic hormone of the pituitary.

6 The material presented provides evidence that mongolism is not associated with a primary congenital pathology of the male and female gonads, but is associated with secondary atrophy and immaturity. It is suggested that the pathology of the gonads is due to the lack of gonadotropic factors from the pituitary and from those glands which influence the gonadal development (adrenal cortex and thyroid)

7. The material presented provides evidence that mongolism is usually not associated with a primary deficiency of the thyroid as is seen in cretinism, but is definitely associated with thyroid pathology. The thyroid is hypoplastic and is more or less a 'resting' colloid goiter. In contrast to the thyroid of cretinism with its inability to produce and store colloid, the thyroid of the mongoloid has this ability, but is inactive because of lack of stimulation. On the basis of the experimental evidence in the literature, it is suggested that the thyroid of the mongoloid is a 'resting' thyroid due to lack of stimulation by the thyrotrophic hormone of the pituitary. In the literature on mongolism, the same types of pathology herein reported have been observed—the hypoplastic, degenerated thyroid, and the colloid thyroid with controversial signs of hyperactivity. On the basis of the material now available, it is safe to state that the thyroid of the mongoloid is hypoplastic and hypofunctioning. Although the colloid storage is sufficient to maintain metabolism at a level of about 80 per cent of the normal and 'short of myxedema,' there are indications that the inactivity of the mongoloid thyroid plays an important part in the pathology of mongolism

8 It is demonstrated that the pituitary of the mongoloid manifests signs of a functional disorder

9 The material presented seems to permit the conclusion that the developmental disorder of mongolism after birth is not the result of a pathologic constitution (a 'mutation'), but is the result of an endocrine disorder of the pituitary body with ensuing functional pathology of the thyroid, adrenals and gonads

10 Prevention of mongolism will always remain the main goal. It is, therefore, important to develop means of detecting threatening mongolism during prenatal care. At birth, the mongoloid child is essentially immature. Sometimes there are developmental anomalies which are not amenable to therapy. In less severe cases the main requirement for treatment is to start before edema of the brain, as well as inadequate metabolism of the brain tissue, have produced irreversible changes. In endocrine therapy the complicated character of the pituitary dysfunction has to be

considered, as well as the tendency of the thyroid to colloid goiter, which is in contrast to the hypothyroidism of myxedema and cretinism. Therapy with the preparations now known is not feasible, but it may be hoped that materials soon will be available the use of which will permit a more encouraging view of the whole problem.

I am deeply indebted to Dr. C. Stanley Raymond, Superintendent of the School, for his interest and unceasing support of our research in mongolism; and to my collaborators in the Wallace Research Laboratory.

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## Suppression of Endocrine Activity by Immunization

THE SUBJECT of antihormones periodically seems to stimulate thought and experimental work directed toward the control of endocrine activity. The practical incentive for much of this work is the relative ease with which hormonal deficiency may be treated by substitution therapy, as contrasted with the complex difficulties often encountered in combating hormonal excess. How may one depress the net activity of an endocrine gland by simple procedures? In a recent issue of *Endocrinology* there appeared a paper by Jacob Lerman entitled "Hormone Action of Thyroglobulin Antibodies" which presents interesting data on this problem and raises several important questions.

The experiments described by Lerman embody two outstanding findings. The first of these is that repeated intraperitoneal injection of human thyroglobulin into a rabbit frequently renders the animal hypothyroid or even myxedematous. The second is that such an animal usually shows a poor response to subsequent injections of thyroglobulin intraperitoneally. These are provocative facts which merit further extension of the work and analysis.

Are the antibodies so produced strictly "antihormonic" or rather "anti protein"? The significance of this distinction is illustrated by a recent report of Francis C. Lowell. He has shown that a patient, both allergic and resistant to crystalline insulin derived from pork and beef pancreas, was allergic but not resistant to human insulin. In this instance it was demonstrated that the patient's serum contained antibodies which physiologically neutralized animal insulin but not human insulin. In other words, the antibodies were "anti-protein" but not necessarily "antihormonic." Similarly Lerman has found that the serum of his immunized rabbits gives a precipitin reaction against a preparation of thyroglobulin (from endemic goiter) which is physiologically inert. Furthermore, thyroglobulin is completely effective when ingested by the immunized animals, which also respond satisfactorily to injected thyroxine.

Therefore, it is not clear how useful such an antiserum might be in combating an excess of thyroid hormone which is already circulating. In Graves' disease, however, in which the source of the hyperthyroidism is endogenous (in the patient's gland), protein-specific antibodies might provide a useful means of suppressing glandular activity on a chemical basis. Such, indeed, is the effect of iodine therapy, but iodine usually is reliable as a practical treatment only for temporary suppression of the thyroid's output of hormone. If carrier-specific antibodies invariably would suppress glandular activity for prolonged periods, a new era in the treatment of endocrine hyperactivity would dawn.

Evidence has been accumulating that endocrine glands may be influenced chemically with resulting decrease in function. To cite one instance, Morgan and Ivy treated 6 young rabbits with intraperitoneal injections of an antiserum prepared by injecting hens with a saline extract of rabbit thyroid. In large doses (10 cc) the serum was lethal. In smaller doses, however, the animals became 'pot-bellied' and apathetic. The hair was lusterless and shaggy. The animals grew very slowly, and some of them died within 3 months. In such cases the thyroids were so small as to be difficult to find at autopsy. These findings, combined with Lerman's determinations of basal metabolic rate, make a good case for the artificial production of myxedema. There are, furthermore, scattered references in the literature which suggest that other endocrine organs may react similarly.

The mechanism at work in the experiments cited is by no means clear. Is it a direct effect upon the thyroid cells, —perhaps that of a cytolytic? Is the pituitary thyrotrophic hormone involved? Does the effect bear any relation to the abrupt although temporary fall in basal metabolism commonly encountered clinically when prolonged heavy dosage of thyroid is suddenly interrupted? Why does the immunized animal fail to respond to injected thyroglobulin if he responds readily to thyroglobulin by mouth and to thyroxine obtained from hydrolyzed thyroglobulin? These are points which require investigation.

It should be pointed out that any attempts at application of these results in the clinic must be made with great caution. Intravenous injection of thyroglobulin frequently may lead to allergic exanthema. Intramuscular or subcutaneous injections of thyroglobulin may cause abscess formation without much effect on serum antibody titer. Intraperitoneal injections in man raise mechanical objections. Passive immunity, however, as suggested by Rogers and Beebe, may be feasible provided serum reactions can be avoided. Detailed descriptions of this clinical method appeared in 1906 and 1909, and again in 1915, covering its use in some 3000 patients. Fifty per cent of the patients so treated were reported to show striking benefit. Nevertheless, the results tended to be not so dramatic or reliable as the combination of iodine and surgery which, simultaneously developed, has yielded such an enviable statistical record in the past two decades.

On the whole, it may be concluded that immunization or highly purified cytotoxic sera offer an intriguing prospect of suppressing endocrine activity specifically. Further studies in animals are needed before a confident approach to safe clinical application can be envisioned. Nevertheless, the observations thus far are sufficiently stimulating and impressive to justify further investigation, particularly of glands other than the thyroid, for which easy therapeutic control is not available.

<sup>1</sup> Lerman, J. *Endocrinology* 31: 558, 1942.



# COMMUNICATIONS TO THE EDITORS

## Androgen Therapy in Women

TO THE EDITOR:

I HAVE READ the letter addressed to you by Dr. E. C. Hamblen,<sup>1</sup> in the September issue (1942) of the *JOURNAL OF CLINICAL ENDOCRINOLOGY*. He is right in criticizing the abuse of the male hormone, testosterone, in females but one should be careful in condemning the general use of a valuable drug just because some practitioners abuse it. Any potent drug used by one who does not know of its dangers and shortcomings is likely to produce undesirable effects. Dr. Hamblen should condemn the improper use of any new drug by such practitioners, but not the drug itself.

In my experience no other single substance is as desirable as the male hormone to stop lactation when that is necessary. It does away with limitation of fluid intake, with bandaging the breasts and painful engorgement. Three or four injections of 25 mg. will suppress the secretions very thoroughly.

There are female patients who will not respond to estrogenic substances but will respond to the androgens, usually in dosage schedules of 25 mg. 3 times during the first week, twice during the 2nd and once a week thereafter.

There seems to be such a thing as an androgenous mosaic, which Dr. Draper describes,<sup>2</sup> which I am sure other men have also observed. After treating cases of menopausal hyperthyroidism with estrogenic substances, we have found some which did not respond to the female hormone but when androgens were substituted we obtained excellent results, there were no flushes, no tremor; the B M R. was lowered and the blood cholesterol was increased.

<sup>1</sup> HAMBLÉN, E. C. *J. Clinical Endocrinology* 2: 575. 1942.

<sup>2</sup> DRAPER, G. *New England J. Med.* 225: 393. 1941.

During the period of 2 or 3 years' observation, a peculiar thing we have observed is that in all of these cases which have reached menopause there was no hirsutism and no change of voice. On the contrary, there is the case of a young unmarried girl who was bleeding excessively; the hemoglobin was very low. She was treated with every drug available; a curettage and a laparotomy were performed. The drug which stopped the bleeding was testosterone, but there was a change in voice and an increase of hirsutes which, however, disappeared a few months later.

I have treated an unmarried woman of 45 who came to me after having been treated with radium for excessive premenopausal bleeding. She was given estrogens and many other drugs but the bleeding and all of the menopausal symptoms persisted. Testosterone was given, with excellent results. She was told beforehand of the possibility of hirsutism and change of voice but neither occurred. At different times, without her knowledge I gave her estrogens. She returned for treatment earlier than usual saying she did not feel so well; she had prolonged bleeding and flushes under the estrogen treatment, while the androgens controlled the symptoms. In none of these menopausal cases did we obtain any masculinizing effects despite the fact that some of the patients were treated for periods as long as 1 to 3 years with the drug.

Gonadotropic hormones have been used in cases in which estrogenic substance should have been used, and vice versa. Potent drugs such as the endocrine preparations should not be used without knowing what is to be expected and the limitations of the therapy.

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## An Error in Terminology

TO THE EDITOR:

May I raise the question of the heading 'Ovarian Dwarfism' applied by the Editor to our paper 'An Association of short stature, retarded sexual development and high urinary gonadotropin titers in women' in the March, 1942, issue<sup>1</sup> of this Journal. This term is Dr. Albright's and not ours, and it carries a specific connotation which we are not prepared to accept. Indeed, Dr. Albright, if I

<sup>1</sup> VARNEY, R. F., A. T. KENYON AND F. C. KOCH: An association of short stature, retarded sexual development and high urinary gonadotropin titers in women. *J. Clinical Endocrinology* 2: 137. 1942.

understand him, has used this term in the spirit of scientific verbal shorthand and has given his own paper on the subject<sup>2</sup> a title nearly as cumbersome as ours. That this heading can readily be regarded as ours is evidenced by Dr. E. K. Shelton's comment on the propriety of the term in his article<sup>3</sup> in the June issue of *Endocrinology*, 1942.

<sup>2</sup> ALBRIGHT, F., P. H. SMITH AND R. FRASER: A syndrome characterized by primary ovarian insufficiency and decreased stature. *Tr. Assoc. Am. Phys.* In press. *Am. J. Med. Sc.* In press.

<sup>3</sup> SHELTON, E. K.: The clinical aspects of dwarfing. *Endocrinology* 30: 1000. 1942.

We would greatly appreciate the publication of this letter in the current volume of the *JOURNAL OF CLINICAL ENDOCRINOLOGY*, so that such of your readers as are interested may understand that we deserve neither the credit

nor the responsibility for the expression 'ovarian dwarfism'.

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## Diagnosis of Simmonds' Disease

TO THE EDITOR

MAY we offer a short comment on the reference in the article by Moss,<sup>1</sup> to the use of two tests (urinary 17 ketosteroid excretion and insulin tolerance test) which we have advocated<sup>2</sup> for the diagnosis of Simmonds' disease. The author remarks that he attempted but failed, with his case 1, to establish the diagnosis by these two tests. While welcoming his interest in the tests, we submit that the evidence, in his excellent clinical description and postmortem report of this case, is against Simmonds' disease having been present. Chronic malnutrition consequent on the frequent vomiting is surely adequate explanation for the clinical features

which had suggested this diagnosis, and the postmortem findings of a relatively normal anterior pituitary serve to bear this out, and confirm the results of the above mentioned tests. There is probably some lowering of anterior pituitary function in malnutrition, but these tests appear to distinguish the more extensive lowering of function which must occur before primary organic disease of the anterior pituitary produces the symptoms of Simmonds' disease.

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<sup>1</sup> Moss R. E. *J. Clinical Endocrinology* 2: 395, 1942.

<sup>2</sup> Fraser R., and P. H. Smith. *Quart. J. Med.* 10: 297, 1941.



# Abstracts of

## CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. Collaborators: E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLIN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

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### ADRENALS

HERMANN, O.

Cholesterol content of adrenals of newborn and sucklings. *Monatschr. f. Kinderh.* 82: 76. 1940.

Considerable variations in the amount of free and bound cholesterol were found. In rickets, weight of adrenals as well as their fat and lipin content were greatly increased. Very high values were found in pyoderma and miliary tuberculosis. Cholesterol values were very low in disturbances of nutrition and in a case of congenital syphilis, the weight of the adrenals was decreased. In dystrophias, high cholesterol values were found. In all pathological cases, the adrenal cholesterol values corresponded generally with those of blood.—*Courtesy Chem. Abstracts.*

TALBOTT, J. H., L. J. PECORA, R. S. MELVILLE, AND W. V. CONSOLAZIO.

Renal function in patients with Addison's disease or adrenal insufficiency secondary to pituitary pan-hypofunction. *J. Clin. Invest.* 21: 107. 1942.

The clinical tests for renal disease were normal in most patients. Rate of formation of glomerular filtrate and tubular reabsorptive capacity for glucose were abnormal. Renal plasma flow was affected less and tubular capacity for excreting diodrast least. The filtration fraction was depressed below normal. Administration of desoxycorticosterone acetate corrected partly, but only temporarily, these deficiencies; adrenal cortical extract had no action. Administration of desoxycorticosterone acetate to two normal persons was without effect on renal activity.—*Courtesy Brit. Chem. and Phys. Abstracts.*

THORSTAD, M. J.

Adrenal apoplexy, *Am. J. Surg.* 55: 44. 1942.

Acute adrenal apoplexy must be considered in the differential diagnosis of an acute abdominal condition. A review of the literature since 1928 revealed twenty-two reported cases of this disease. Two additional cases of unilateral adrenal apoplexy in the adult are presented.

Suprarenal hemorrhage may occur unilaterally or bilaterally, the latter being the more common, there being marked variations in the extent of the hemorrhage from scattered areas with little destruction of the parenchyma to conversion of the entire gland into a blood sac. The disease may be characterized by acute abdominal symptoms by general asthenia or by delirium, convulsions and

coma. There are no pathognomonic signs or symptoms and a diagnosis is difficult to make. Treatment is largely supportive supplemented by the surgical removal of the adrenal in unilateral apoplexy.—*Author's summary.*

### ENDOCRINE GENERAL

ASCHHEIM, S.

Simplified method for biological diagnosis of pregnancy. *J. Lab. clin. Med.*, 27: 547. 1942.

Two female immature rats, 4-5 weeks old, receive 1 subcutaneous injection of 0.5 cc. of the urine. Vaginal smears of both rats are made 72-84 and 96 hrs. after. In pregnancy, only epithelial cells without free mucus or leucocytes are found in the vagina after 72 (often 66) hours. After 84-96 hours keratinized cells (seldom mixed with a few epithelial cells) are found which are the criterion of a positive reaction.—*D.A.M.*

BRONSTEIN, I. P., J. A. LUHAN AND W. B. MAVRELIS.

Sexual precocity associated with hyperplastic abnormality of the tuber cinereum. *Am. J. Dis. Child.* 64: 211, 1942.

A case of sexual precocity in a twenty-two month old girl is reported adding another to the 17 cases of precocious puberty and hypothalamic tumors collected by Weinberg and Grant in 1941. Death occurred through an accidental meningitis and necropsy revealed a small tumor-like mass beneath the floor of the third ventricle, between the infundibulum and the mamillary bodies. The structure of this hyperplastic malformation was not unlike that of the tuber cinereum. There was a relative eosinophilic hyperplasia of the pars distalis of the hypophysis.—*M.B.G.*

BROWN, W. E.

Treatment of gonorrheal vulvovaginitis with estrogens. *Am. J. Dis. Child.* 64: 220, 1942.

Persistent cornification of the vaginal epithelium is necessary for cure of gonorrheal vulvovaginitis and its absence is responsible for many of the reported failures with estrogens. The author reports bacteriological and clinical cures in 19 cases in girls, 13 of which were gonococcal and 6 non-specific in origin. Sulfanilamide or derivatives were unsuccessful. No complications were encountered.—*M.B.G.*

DOBRINER, K, E GOROON, C P, RHOADS, S LIEBERMAN  
AND L F FISER

Steroid hormone excretion by normal and pathological individuals *Science* 95 534 1942.

Urine was collected over a 6 month period from 6 normal persons, 6 patients with cancer, one with cancer of the adrenals and 4 with clinical evidence of adrenal hyperplasia. After hydrolysis, urine was fractionated into acidic, phenolic and neutral fractions. Neutral fractions were separated into ketonic and non-ketonic fractions, each of these being further separated with digitonin into 3-alpha and 3-beta-ketosteroids. Excretion of total ketosteroids, 10-20 mg per day in normal persons, 5-10 mg in cancer patients, 40-60 mg in adrenal hyperplasia and 285 mg in the patient with adrenal cancer. Of the total ketosteroids, the percent excretion of beta-ketosteroid was 0.6-2.2 in normals, 0.3-6.0 in cancer patients, 3.7-11.4 in adrenal hyperplasia, and 66.0 in the patient with adrenal cancer. Further fractionation of alpha-ketosteroid fractions yielded androstosterone-17, androstosterone, 3-alpha-hydroxycholestan-17-one and 4 unidentified steroids as well as impure substances. Proportions in all patients and in normal subjects are presented —D A M.

EVANS, H M AND A GORSMAN.

Urinary gonadotropins in normal men *Proc Soc Exper Biol & Med* 49 674 1942

A modified alcohol precipitation method is described for preparation of non-toxic gonadotropic concentrates from normal male urine. Assayed in female immature rats, such concentrates of pooled samples of urine from healthy college men gave titers of 10 to 45 rat units per liter. In normal female mice the titers were 6 to 20 mouse units per liter. Assayed in hypophysectomized rats, the concentrates produce follicle stimulation and interstitial cell repair at the same dosage level, although in some cases, follicle stimulation may be produced at dosage levels as low as one-third that required for interstitial cell repair —*Courtesy Chem Abstracts*

Foss, G L

Implantation of sex hormone tablets in man *J Endocrinol* 3 107, 1942

Weighed tablets made from compressed crystals of estrone, estradiol, testosterone propionate, testosterone and progesterone were implanted in male and female patients subcutaneously. At varying periods of time, these were removed and weighed. The average rate of absorption increased in the order given, tissue reactions varying directly with the rate of absorption —*Courtesy Chem Abstracts*

DIAZ MINDURRY, EUGENIO F.

Cardiac neurosis and endocrine function *Semana med* 49 1159 1942

Complaint of patients of palpitations, arrhythmias and precordial pain with or without irradiations is often ac-

companied only by insignificant objective findings such as extrasystoles, tachycardia, while heart sounds, blood pressure, electrocardiogram and X ray examination reveal nothing unusual. The striking feature is a peculiar psychic disturbance that either precedes the heart symptoms and induces their appearance following constant self-observation or finds its origin in primary minor heart irregularities. The malicious circle that follows develops often on an endocrine basis. Hyperfunction of the thyroid may be the determining factor without any of the typical symptoms of Graves' disease. The metabolic rate is the most important diagnostic help in these cases. Treatment consists in avoidance of all psychic and chemical stimulation (coffee, alcohol, etc.) administration of diiodotyrosine in series of 20 days' treatment, and insulin, 10 to 20 units 30 minutes before breakfast with or without the addition of carbohydrates. Adrenocortical deficiency is difficult to diagnose. It is characterized by asthenia, loss of weight and often by enteropostis. The blood sugar is subnormal and the response to 10 units of insulin is enhanced. The ascorbic acid and cholesterol in the blood are low but K and Na are not sufficiently affected to be of diagnostic value. Treatment with desoxycorticosterone is valuable. In the menopausal estrogen deficiency parenteral doses of 1 to 5 mg of estrogen 1 to 3 times weekly may be given or 10,000 units several times daily orally. In the premenopausal deficiency the doses should not exceed 500 to 1,000 units daily to avoid metrorrhagias —A E M.

NATHANSON, I. T.

Treatment of mammary pain and secretion with testosterone propionate *New Eng Jour. Med* 226 323 1942

Testosterone propionate was administered to 30 carefully selected patients with severe mammary pain and secretion. Relief occurred in a high percentage of the cases, effectiveness of this treatment being definitely better than with estrogens. Recurrence of symptoms is a rule usually within 6 months after discontinuance of treatment. Prolonged and continuous treatment is not recommended and care must be exercised in selection of cases presenting psychogenic elements —D A M

RABINOW, M

Appearance of ossification centers. Groupings obtained from factor analysis *Am J Dis Child* 64 229, 1942

The ages were determined at which certain centers of ossification appeared in a group of 31 children. These data were interrelated and subjected to factor analysis. The analysis yielded three factors, a "round bone" factor, an "epiphysis" factor and a third factor which was possibly an artefact. The author suggests that bone development be expressed on the basis of "round bone skeletal age" and "epiphysis skeletal age." It is possible for the carpals and tarsals to be normal in time of appearance and maturation and for the epiphysis to be retarded and vice-versa —M B G.

RANDALL, L. M. AND M. H. POWER.

Amounts of glycogen in endometrium *Proc Staff Meet, Mayo Clin* 17 158. 1942.

Glycogen concentration of endometrial tissues vary with the different phases of the menstrual cycle. Four specimens showing only proliferative phase on microscopic examinations showed an average of 0.171 per cent glycogen. Three specimens from late proliferative and early differentiative phases of the endometrium contained an average of .35 per cent glycogen. Six specimens from early differentiative phase averaged .109 per cent glycogen. Seventeen specimens in the late differentiative phase contained .71 per cent glycogen.—D A M.

ROBINSON, M.

Investigation of breast feeding; a study of 1,000 mothers. *Arch Dis Childhood*, 17 23 1942.

Breast-feeding is not affected by the following season of the year, parity or the age of the mother, size of the breasts, antenatal presence of secretion in the breasts, return of menstruation, rheumatic endocarditis, simple enlargement of the thyroid, pre-eclampsia, and antenatal symptoms relieved by Ca. Breast-feeding is affected by the size and character of the nipple, masculinity, obesity, morning sickness, pyelitis, severe varicose veins, breast abscesses and cracked nipple. 52% of early weaning occurs in all types before the end of the first month.—*Courtesy Brit Chem and Phys Abstracts*.

STURGIS, S. H

The use of stilbestrol in the relief of essential dysmenorrhea *New England J Med* 226 371. 1942

Daily doses of 1 mg diethylstilbestrol is given orally for a period of 20 days beginning at least three weeks before the expected onset of menstruation as recorded from a number of previous menstrual cycles. This therapy primarily inhibits the follicle stimulating hormone of the pituitary and secondarily suppresses growth of ovarian follicles and ovulation. After discontinuance of treatment, normal cycles are re-established with the invariable recurrence in about one month of typical dysmenorrhea. In 20 per cent of patients, treatment must be discontinued because of gastrointestinal complaints. Estrogen therapy for essential dysmenorrhea is of value as a temporary rather than permanent form of relief.—D A M.

TIEN, D S P.

Significance of pregnanediol in pregnancy urine *Chinese M J* 59: 416 1941.

Excretion of pregnanediol by Chinese women at various stages of gestation corresponds with that described in Western women. It is premature to regard excretion of pregnanediol as an accurate index of corpus luteum activity. In twin pregnancy, pregnanediol excretion was abnormally high throughout. Isobutyl alcohol is inferior to normal butyl alcohol as an extraction solvent.—*Courtesy Chem Abstracts*.

## GONADS

BELL, G. H.

The behavior of the uterus of the rhesus monkey under the influence of certain hormones *J. Endocrinol* 3 87 1942

Effects of various hormones on uterine movements of ovariectomized animals were recorded. Animals received estrone in oil, estrone followed by testosterone and estrone followed by progesterone. Spontaneous reactivity, in vivo, and reactivity due to oxytocin injections were variable in all groups and in untreated controls and showed practically no difference between groups except that contraction waves were low in the estrone-testosterone group and somewhat slower in the estrone-progesterone treated group. Vasopressin produced relaxation in all groups. Comparison of these results with the recorded behavior of the human uterus is discussed.—D A M

BYRNE, W. H., J C WEED, B B WEINSTEIN AND C G. COLLINS.

Vitamins and stilboestral in treatment of hypo ovarianism *New Orleans Med J.* 94: 330 1942

Report of 57 cases with menopausal symptoms. The addition of a combined vitamin preparation did not lessen the incidence of nausea.—*Courtesy Brit Chem and Phys Abstracts*.

FERRIS, D. O.

Pathology of tumors of the testis: correlation with excretion of hormone in the urine. *Proc Staff Meet, Mayo Clin.* 16 615. 1941.

Increased amounts of urinary gonadotropin are found in all cases of malignant tumors of the testis. Using the method of Frank (1935), the author finds that values below 20 rat units per liter may be considered nonpathologic whereas those above this value are presumptive of pathology.—D A M

HECKEL, N J. AND H L KRETSCHMER.

Carcinoma of the prostate treated with diethylstilbestrol *J A M A* 119 1087 1942.

The carcinoma of the prostate softened under diethylstilbestrol treatment—3 to 12 mgm daily. The patient gained weight and the subjective symptoms disappeared. Histologically the neoplastic cells showed hydropic degeneration and vacuolization.—C C P.

WEINHOUSE, G. AND J. I. BREWER.

Cyclic variations in the lipids of the corpus luteum *J. Biol. Chem* 143 617. 1942

Free cholesterol remains relatively constant throughout all stages of development of the human corpus luteum. Cholesterol esters remain constant or decline slightly with increasing activity, reaching lowest values in actively functioning corpus luteum of pregnancy. In the regressive phase, cholesterol esters increase to five times their value during functional periods. Phospholipids increase gradually with age of the organ reaching maximal values during

maximal function. They decline slightly during regression. Glycerides do not vary appreciably during development of the corpus luteum but large increases occur during regression. Cyclic changes in phospholipids are not accompanied by significant changes in relative proportions of lecithin, cephalin or sphingomyelin.—*Courtesy Chem Abstracts*

## HYPOPHYSIS

JEFFERS, WM A, MARY M LIVEZEY AND J H AUSTIN

A method for demonstrating an antidiuretic action of minute amounts of pitressin. Statistical analysis of results. *Proc Soc Exper Biol and Med* 50 184, 1942

Rats are made diuretic by giving water by stomach tube, the water containing sufficient alcohol to produce mild sedation. 20 microunits (0.0002 units) given intravenously produce detectable antidiuretic effects.—D A M

## PANCREAS

BARNARD, R D

Insulin ferrihemochromogen. *J Lab & Clin Med* 27 774 1942

Insulin combines with ferriheme (hematin) in anhydrous ammonia forming various insulin ferriheme conjugates depending on the proportions of reacting components. These ferrihemochromogen compounds are water soluble and are physiologically active, those of the lower insulin to ferriheme ratios showing a prolonged and delayed action similar to that produced by depot forms of insulin. No clinical data are presented.—*Author's abstract*

BERG, MAX

Absorption of intracutaneously injected solutions of dextrose and sodium chloride. Comparison of absorption time for diabetic and non diabetic subjects. *Arch Int Med* 69 99 1942

In 173 observations on 3 groups, persons with uncontrolled diabetes, persons with controlled diabetes and on non diabetic subjects, absorption rates of intracutaneous injections of various solutions including 85% saline, 0.1% and 5% glucose and 1.7% urea, were studied.

Despite relatively wide ranges of fluctuations in actual absorption times for individual tests, definite differences were observed between the ratio of absorption times of various solutions of glucose to the absorption time of saline for persons with uncontrolled diabetes and for persons with controlled diabetes. The latter ratio was similar to that of normal subjects.

Differences could not be explained by states of hydration but were related more directly to permeability of skin.—D A M

COLWELL, A R, J L IZZO, AND W A STRYKER

Intermediate action of mixtures of soluble insulin and protamine zinc insulin. *Arch Int Med* 69 931 1942

1 Suitable mixtures of the 2 standard insulins may be prepared which show any desired intermediate action between the 2 in promptness, intensity and duration of effect. 2 Such intermediate effects gain intensity and

promptness at the expense of prolongation of action. The converse is also true. 3 Intermediate effects which are decisive cannot be obtained with simple mixtures of the 2 insulins until as much soluble insulin as protamine zinc insulin is used in them. 4 Probably mixtures containing more regular insulin than protamine zinc insulin, possibly 2 or 3 times as much, are most suitable for daily use in the treatment of severe diabetes. 5 Such mixtures owe their intermediate effects to reduction in the amount of protamine, zinc or alkaline buffer. There is evidence to indicate that insulin in a different physical or chemical form is responsible for the modified action rather than composite effects from simple fractions of soluble insulin and insoluble protamine zinc insulin. 6 Results of treatment with these modifications suggest that better control of severe diabetes mellitus may be obtained with single daily doses of 1 of them than with protamine zinc insulin or unmodified insulin given alone or both administered simultaneously in separate doses. Multiple injections may be avoided and dosage reduced because of greater efficiency.—I B

GLASS, W L, C L SPINGARN, AND H POLLACK

Unusually high insulin requirements in diabetes mellitus. Report of a case. *Arch Int Med* 70 221 1942

A case is described of diabetes mellitus in which the insulin requirement was more than 85,000 units of insulin in a 5½ month period of observation. During episodes of ketotic acidosis it was necessary to give 2,360 units, 2,500 units and 2,795 units of insulin in 24 hours before adequate control was accomplished. No definite cause for the insulin refractory state could be determined. Therapeutic procedures included roentgen irradiation over the pituitary and the administration of lipocaine. It was not possible to establish a definite relation between these forms of therapy and the improvement which followed their use. The excessive insulin need subsided 6 months after its onset, and the patient remained mildly diabetic for the subsequent 6 months.—I B

JOSLIN, E P, H F ROOT, P WHITE AND A MARBLE

Diabetic coma. *JAMA* 119 1160 1942

In the past two years 62 consecutive cases of diabetic coma were successfully treated by prompt and energetic use of large doses (200 units in 2 hours) of insulin. Supportive measures were: (1) Adequate saline therapy to overcome dehydration, (2) Routine gastric lavage to relieve persistent distention, and (3) Constant intravenous infusion of fluid, plasma or blood to restore blood volume and support the circulation. No dextrose or alkali was used. Previous to the institution of the above therapeutic regime the mortality had been 11%.—CCP

KERWIN A J

Fatal hyperinsulinism with cerebral lesions due to pancreatic adenoma. *Am J Med Sci* 203 363 1942

A case of fatal hyperinsulinism due to multiple islet cell tumors of the pancreas is reported. The patient died 16 days after the onset of the first symptoms and after 8 days of continuous coma. The tumor contained 30 units

of insulin per g. of tissue. The brain showed congestion, edema, hemorrhages, nerve cell degeneration, and gliosis, but these changes were not severe.—*Courtesy British Chemical and Physiological Abstracts.*

LOZINSKI, E. AND L. I. FROHLICH

Resistance to insulin. *Canad. M. A. J.* 46: 62. 1942.

A case of resistance to insulin is described in whom 3000–4000 units of insulin daily were required to prevent hyperglycemia, acidosis, and coma. There was no evidence of the presence of an anti-insulin or insulin-destrating substance in the patient's serum or of insulin excretion in the urine. Irradiation of the pituitary gave a satisfactory response.—*Courtesy British Chemical and Physiological Abstracts.*

## PARATHYROID

ANDERSON, G. W. AND L. MUSSELMAN.

Treatment of tetany in pregnancy with a brief review of literature. *Am. J. Obst. & Gynec.* 43: 547. 1942.

A review of 240 reported cases of tetany in pregnancy is presented. These were classified in 4 types: 26 were of the postoperative hypoparathyroid type of tetany with pregnancy; 145 were of the idiopathic or spontaneous type including those occurring during pregnancy, in labor or post partum. A third group of 9 cases due to low Ca intake and vitamin D deficiency is reviewed. The last group included 60 cases associated with thyroid deficiency disease. Relationships of tetany to menstruation, lactation, blood loss at delivery, hyperventilation and low Ca intake is discussed. Past and modern treatment is reviewed. The latter consists of oral and intravenous Ca, parathyroid hormone and dihydrotachysterol. Of 3 cases of the postoperative type treated by the author, two went to successful term. Therapeutic abortion was necessary in one because of pre-eclamptic toxemia.—*Author's abstract.*

HARDING, F. E.

Use of dihydrotachysterol in parathyroprivic tetany. *J. Lab. Clin. Med.* 27: 497. 1942.

Treatment of a case of parathyroprivic tetany with injury to the recurrent laryngeal nerve is described. The nerve regenerated in a few months, but deficiency in parathyroid hormone continued after 1½ years. Maximal improvement occurred with intensive treatment with low P diet, Ca gluconate, irradiated ergosterol, dihydrotachysterol and thyroid extract. Dihydrotachysterol (1 cc. daily) raised the blood Ca, prevented tetany and partly decreased laryngeal stridor. Thyroid extract raised the B.M.R. and further improved the laryngeal stridor.—*Courtesy Brit. Chem. and Physiol. Abstracts.*

WOO, T. T., C. FAN AND F. T. CHU.

Treatment of infantile tetany with dihydrotachysterol. *Chinese M. J.* 60: 99. 1941.

Serum Ca was restored to normal levels and tetany relieved in 4 of 5 infants by A.T. 10 in daily doses of 1.0

to 1.5 cc. for 1 to 4 days. The resistant case, which had a very low serum Ca, responded to vitamin D.—*Courtesy Brit. Chem. and Physiol. Abstracts.*

## THYROID

BREIDENBACH, L. AND E. APPELBAUM

Masked hyperthyroidism. *Ann. Surg.* 115: 184. 1942.

Great emphasis was laid on the importance of bearing in mind the possibility of thyrotoxicosis when a patient presents an atypical clinical picture of some other type of disease, particularly organic heart disease, with or without congestive heart failure, angina pectoris or auricular fibrillation, diabetes mellitus, hypertension, some form of gastro-intestinal disturbance, or a psychoneurosis.

Diagnosis of masked hyperthyroidism, in addition to the points mentioned, is based on certain suggestive signs and symptoms as persistent moderate tachycardia, unexplained weight loss, an increase in the basal metabolic rate, improvement or relief of symptoms, decrease in the basal metabolic rate following iodine medication and thyroidectomy, and, finally, the histologic report of the removed gland.—*Authors' summary.*

HERTZ, A. AND A. ROBERTS.

Use of radioactive iodine in differential diagnosis of two types of Graves' disease. *J. Clin. Invest.* 21: 31. 1942.

The ophthalmopathic type of Graves' disease patient excretes more I from a 2 mg. (or less) test dose and takes up less in the thyroid than the classic Graves' disease patient. The urinary I excretion can be used as a diagnostic aid in distinguishing the two types of patients.—*Courtesy Brit. Chem. and Phys. Abstracts.*

HERTZ, S., A. ROBERTS AND W. T. SALTER.

Metabolism of iodine in Graves' disease. *J. Clin. Invest.* 21: 25. 1942.

In 22 thyrotoxic patients and 2 normal persons, urinary excretion, thyroid uptake and retention, and chemical distribution of the thyroid-I were studied using radioactive I. The largest percentage uptakes in the thyroid were at low dosage levels of I. Pre-iodinization decreased subsequent thyroid-I uptake. The hyperplastic thyroid of Graves' disease may take up 80 per cent or more from a sufficiently small dose (2 mg.); urinary excretion accounts for most of the remainder. Analysis of the thyroid after operation for thyroxine-like and non-thyroxine-like fractions showed the labelled I to be increasingly in the former fraction as the time following administration increases.—*Courtesy Brit. Chem. and Physiol. Abstracts.*

HEYD, C. G.

Mortality and morbidity in surgery of the thyroid. *Am. J. Surg.* 60: 18. 1942.

In a series of 652 resections of the thyroid for all surgical conditions there were eighteen deaths or an overall mortality of 2.7 per cent: of these fifteen were carcinomata with three deaths.

Graves' disease contributed 44 per cent of the material, toxic adenomas 16 per cent, nontoxic adenomas 36 per cent, thyroiditis, including Riedel's struma, 1.5 per cent, and malignancy 2.3 per cent. The contrast between Graves' disease and toxic adenomas is marked in many details. The average age of this latter group was forty-four years as against thirty-four years for the Graves' disease group, and less than 5 per cent had eye signs. Furthermore, the average basal metabolism was +31 for toxic adenomas as contrasted with +46 in the Graves' disease group.

Approximately 3% of the cases of Graves' disease had a recurrence of hyperthyroidism and approximately 3% came from other clinics, making an overall of recurrent hyperthyroidisms of 6%.

Approximately 50 per cent of the cases of toxic adenomas have cardiac symptoms and at least half of these have definite organic heart disease. The degree of heart impairment is directly proportional to the chronicity of the hyperthyroidism and some of the most brilliant results in thyroid surgery are obtained in the patients with thyrotoxic heart conditions from toxic adenomas. The operative risk in this group of patients is great, but if a patient with a thyrotoxic heart is able to be on his feet and walk about, he is usually able to survive a thyroid resection after adequate preoperative treatment and rest in bed.—*Author's summary*

PRESTON, F. W. AND W. O. THOMPSON

Persistence and recurrence of toxic goiter following subtotal thyroidectomy. *Arch. Int. Med.* 69: 1019, 1942.

Of 294 patients with toxic goiter undergoing subtotal thyroidectomies during the period 1930 to 1939 and followed up from 3 months to 10 years after operation, 39 showed definite clinical evidence of postoperative thyrotoxicosis. Of this number, 37 were among 212 patients with exophthalmic goiter (17.5 per cent) and 2 among 82 patients with toxic adenoma (2.4 per cent). The thyrotoxicosis was usually less severe than before operation, although in 3 patients it was more severe. In 22 of 33 patients on whom the observation was made it was found that postoperative thyrotoxicosis could be adequately controlled with iodine alone. In 11 of these patients who had a persistence of the disease, permanent remission was observed between 4 months and 3 years after operation. There was a rough parallelism between the amount of thyroid tissue palpable after operation and the degree of postoperative thyrotoxicosis, although there were im-

portant exceptions to this rule. Thus regeneration of thyroid tissue was observed in 74 per cent of patients with postoperative thyrotoxicosis but in only 15 per cent of those without thyrotoxicosis after operation. Of the patients as a whole, regeneration was observed in 22 per cent. Two main factors are responsible for thyrotoxicosis following subtotal thyroidectomy for toxic goiter: (1) the failure of the operation to remove the cause of the disease, and (2) the removal of too little thyroid tissue. It is probably desirable to reoperate on all patients with postoperative thyrotoxicosis in whom the basal metabolic rate cannot be held at or near the standard normal level (below plus 15 per cent) by the administration of iodine. Postoperative administration of iodine will not prevent the regeneration of thyroid tissue. The course of postoperative thyrotoxicosis, including its tendency toward remissions and relapses, resembles the course of the untreated disease.—*I. B.*

SOLEY, M. H.

Exophthalmos in patients with various types of goiter. *Arch. Int. Med.* 70: 206, 1942.

According to the studies reported here, the eyes of patients with nontoxic nodular goiter are no more prominent than those of normal persons. Patients with toxic nodular goiter tend to have more prominent eyes than normal persons but not as prominent as patients with toxic diffuse goiter. The eyes of patients with toxic diffuse goiter are significantly more prominent than those of normal persons or of patients with nontoxic nodular goiter. The eyes of over 50 per cent of the patients with toxic diffuse goiter become measurably more prominent after subtotal thyroidectomy, they become less prominent in only a small percentage of persons. These observations are contrary to the opinion of most surgeons who have relied on clinical impressions as to the state of exophthalmos before and after treatment. It is apparent that loss of the stare associated with hyperthyroidism does not necessarily mean a decrease in exophthalmos. The eyes of thyrotoxic patients treated by roentgen rays show less tendency to increase in prominence. It is suggested, therefore, that for patients with hyperthyroidism in whom exophthalmos is severe, roentgen therapy is more desirable than surgical subtotal thyroidectomy. Furthermore, it is advised that the treatment in this particular group be directed toward preventing the occurrence of malignant exophthalmos.—*I. B.*





# ASSOCIATION NOTICE

## Announcement of the Annual Meeting

*The meeting herein announced will be held contingent upon authorization by the Office of Defense Transportation.*

THE TWENTY-SEVENTH ANNUAL MEETING of The Association for the Study of Internal Secretions will be held in Cleveland, on Monday and Tuesday, April 5 and 6, 1943. The Hotel Cleveland will be headquarters for registration and for the scientific and business sessions. Room reservations should be made early with the Hotel Cleveland.

The Chairman of the Local Committee is Dr. E. Perry McCullagh, Cleveland Clinic, Cleveland, Ohio.

### PRESENTATION OF PAPERS

1. The title of the paper and four copies of a comprehensive abstract must reach the President, Dr. E. Kost Shelton, 921 Westwood Boulevard, Los Angeles, Calif., not later than February 10, 1943.

Abstracts submitted should be in proper form for printing in *ENDOCRINOLOGY*. Not more than the first 200 words can be included in the printed abstract.

2. Non-members who wish to present papers must have titles and abstracts introduced by members.

3. The abstracts of papers will be considered by the Program Committee and the final program announced about March 10, 1943.

4. Papers will be limited to ten minutes for presentation. A ten-minute presentation is designed for condensed discussion of new investigations, either in laboratory or clinical phases of endocrinology. Previous publication or presentation before other societies of national membership may be cause for omitting a paper from the program.

5. Papers presented at the Annual Meeting may be submitted for publication to the Editor of *ENDOCRINOLOGY* or the *JOURNAL OF CLINICAL ENDOCRINOLOGY*. Such submission is invited. Acceptance of a paper for the program does not necessarily mean its acceptance for publication.

You are invited to bring this announcement to the attention of your colleagues and associates who have endocrine research in progress.

### NOMINATION OF OFFICERS

The By-Laws of the Association provide that nominations for all elective offices shall be made by a Nominating Committee and forwarded to the Secretary at least sixty days before the annual meeting. The Nominating Committee for the current year,

appointed by the President and accepted by the Council, is as follows:

Dr. E. Perry McCullagh, *Chairman*, Cleveland Clinic, Cleveland, Ohio.

Dr. C. N. H. Long, Yale University School of Medicine, New Haven, Connecticut.

Dr. Warren O. Nelson, Department of Anatomy, Wayne University, Detroit, Michigan.

The By-Laws also provide (Article V, Section 2) that "Any member of the Association may submit nominations to the Nominating Committee for its consideration." Nominations may be sent to the Chairman, Dr. E. Perry McCullagh, before Feb. 1, 1943.

The terms of the following officers expire at the time of the Annual Meeting in Cleveland in 1943:

|                            |                 |
|----------------------------|-----------------|
| <i>President-Elect</i>     | Carl R. Moore   |
| <i>Vice-President</i>      | John C. Burch   |
| <i>Secretary-Treasurer</i> | Henry H. Turner |

### Council Members

P. E. Smith M. A. Goldzieher George W. Thorn

### Publication Board

E. C. Hamblen Carl R. Moore

### THE E. R. SQUIBB & SONS AWARD

The E. R. Squibb & Sons Award of \$1,000.00 was established in 1939, and was given first in 1940 to Dr. G. W. Corner, in 1941 to Dr. Philip E. Smith, and in 1942 to Dr. Fred C. Koch. A special Committee of five members of the Association chooses an investigator or investigators in the United States or Canada for one of the best contributions to endocrinology.

### THE CIBA AWARD

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than 35 years of age in the field of endocrinology was established last year, but no recipient was selected due to lack of time. The work cited may be either in the field of pre-clinical or clinical endocrinology. The Award is for \$1200.00. If the recipient should choose to use the Award toward further study in a laboratory other than that in which he is at present working, the Award will be increased to \$1800.00. The option is left entirely to the recipient.

Each member has the privilege of making one nomination for each Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions in endocrinology and by a bibliography of the nominee's most important publications, and reprints if possible. Five copies should be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, not later than February 1, 1943.

E. Kost Shelton, *President*  
Henry H. Turner, *Secretary*

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